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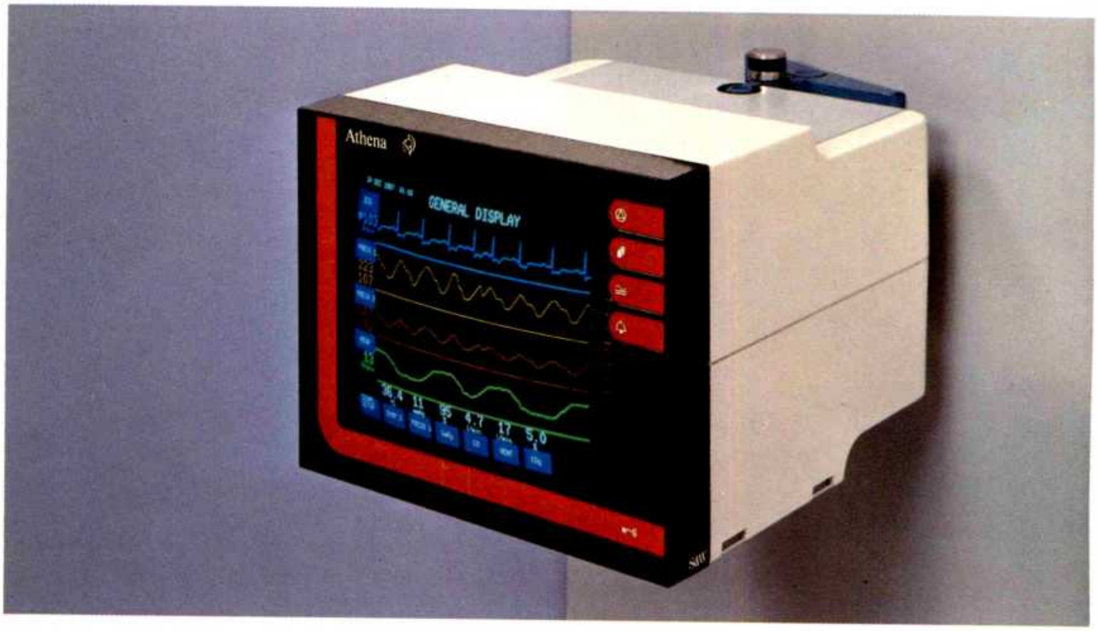

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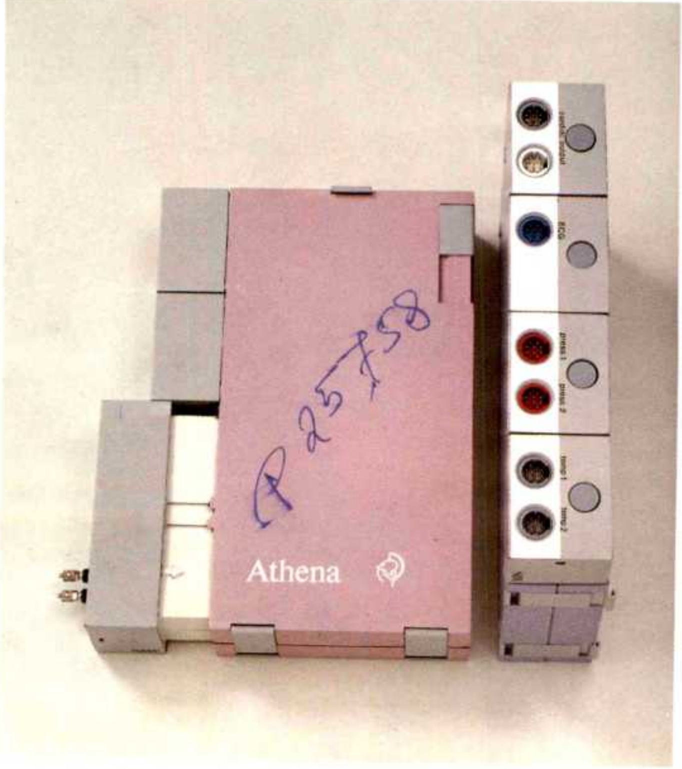

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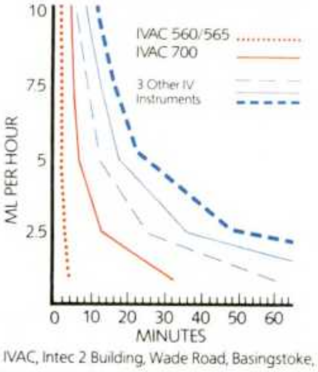

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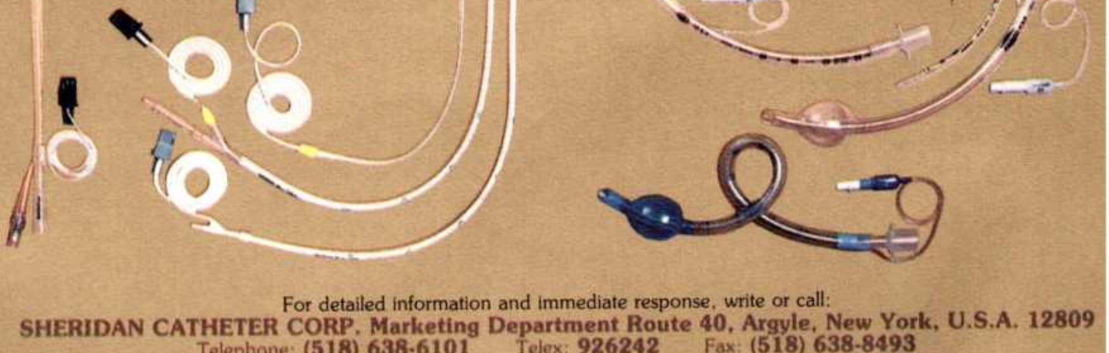

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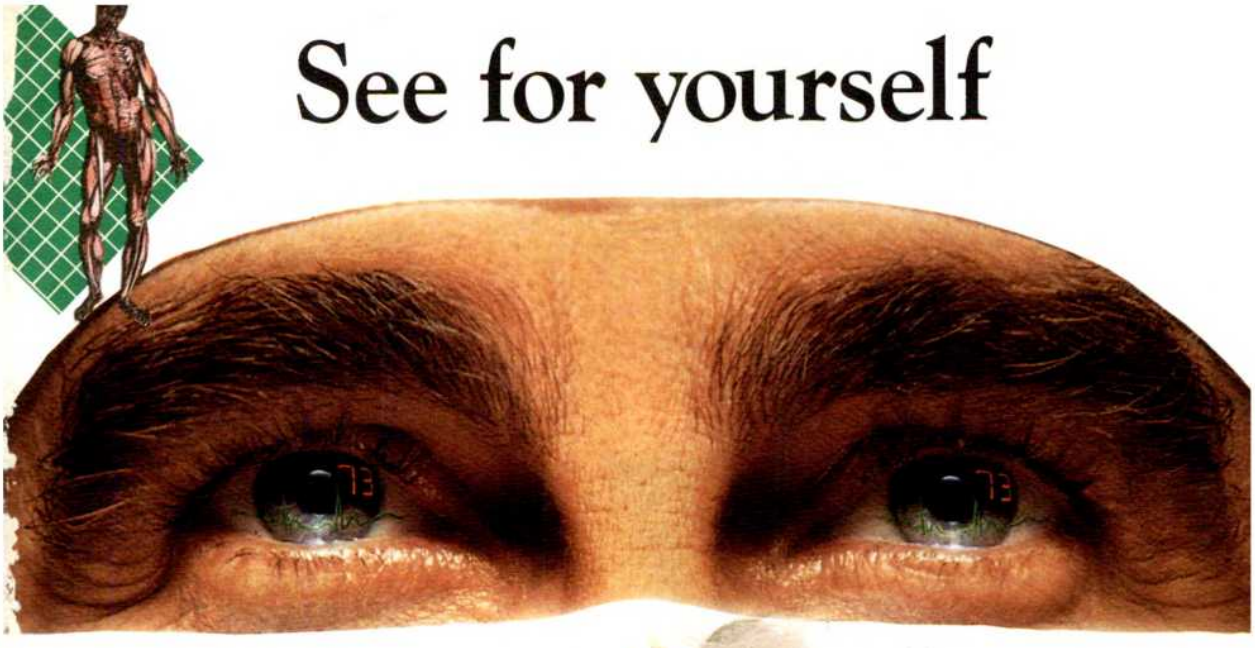

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 61, No. 3 SEPTEMBER 1988

EDITORIAL

FETAL WELL-BEING AND MATERNAL AWARENESS

One of the major problems in the practice of obstetric anaesthesia has been the conflicting requirements of the two patients—up to the time of delivery—when general anaesthesia is provided for operative delivery (currently almost invariably by Caesarean section). The mother wishes to be rendered and to remain unconscious; the infant to be spared the effects of depressant drugs derived transplacentally. However, an additional requirement is for both patients to be sustained in biochemical stability, which in this context may be related simplistically to acid–base and respiratory gas status.

During the 1940s and 1960s, most attention and effort were directed to minimizing "drug induced depression" of the neonate. One consequence was a high incidence of maternal awareness. It seems probable that the pendulum has now swung in the opposite direction. This movement was initiated probably by Moir's demonstration [1] that maintenance of anaesthesia with an inspired mixture containing 0.5 % halothane in 50 % oxygen could ensure maternal unconsciousness (or at least, lack of recall after operation) without harm to the neonate. Indeed, there is what some might term a rather cavalier approach which suggests that the small mass of a volatile inhalation agent reaching the fetus during the interval between induction of anaesthesia and delivery is of little or no consequence to the ultimate well-being of the infant [2] and that the maternal stress response likely to be evoked by awareness is potentially much more harmful to the infant [3].

As a consequence, maternal awareness during Caesarean section should have been virtually eliminated from current practice. Discounting the very unusual case in which the mother requires vigorous intraoperative resuscitation (massive haemorrhage or severe bronchospasm, for example), or instances of technical mismanagement, there are classically three periods when awareness has occurred: during or shortly after tracheal intubation (which usually implies that the anaesthetist has administered an inadequate dose of induction agent [4]); during insertion of the final skin sutures (the anaesthetist has been in a hurry to get away from the theatre or to press on with the list); and at the time of delivery (insufficient volatile agent has been provided). The former two have always been unforgivable. In the light of current practice referred to above, the third situation should no longer occur.

So much for drug related effects, but what of biochemical problems? Much of the danger of asphyxia to which the abdominally delivered infant was exposed 2–3 decades ago (especially if the induction–delivery (I–D) interval was prolonged) has been averted by the avoidance of maternal aorto–caval compression, accomplished usually by the provision of a lateral tilt, although it is recognized that prolongation of the uterine incision to delivery (U–D) interval can, under the conditions of general anaesthesia, promote fetal asphyxia [5]. What is not yet clearly defined is the influence upon the neonate of the choice of oxygen concentration in the maternally-inspired mixture.

For many years standard teaching was based upon the advice of Rorke, Davey and Du Toit [6] and Marx and Matteo [7], although it is likely that, in practice, it has been honoured more in the breach than in the observance. Briefly, it was advocated that nitrous oxide should be administered in a concentration of 33 % in oxygen, the objective being to maintain a maternal arterial Po_2 of approximately 40 kPa. Values less than this were associated with diminished fetal oxygenation. A further increase in maternal hyperoxia produced feto–placental vasoconstriction and thus, again, reduction in fetal oxygenation. Baraka [8] agreed with the first part of this teaching, but reported that increasing the inspired concentration of oxygen from 50 to 100 % was associated with no change in fetal oxygenation.

As the authors of the two articles in the present issue point out [9,10], current understanding suggests that these studies were seriously flawed. Relief from aorto–caval compression was not ensured by Rorke and colleagues [6] and Baraka [8]; little significance was attached to the duration of the I–D and U–D intervals in the control groups of subjects used for comparison, and the technique of anaesthesia was not standardized. Furthermore, no attention was paid to the effect of carbon dioxide. It has been suggested [11,12] that a result of maternal hypocapnia is a reduction of fetal Po_2 and an increase in fetal base deficit and lactic acid concentration. Duncan and colleagues [13] claim that the provision of a fresh gas flow equivalent to 100 ml kg^{-1} min^{-1} guards against maternal hypocapnia and hypercapnia.

The questions therefore remain, what is the optimum concentration of oxygen to be delivered to the mother, and is there a maximum beyond which no benefit derives to the fetus? Oxygen is transferred from maternal to fetal blood almost entirely in response to a pressure gradient. However, the system is rendered more complex by the presence of counter-currents which characterize the anatomy of the intervillous space, and also by the possibility that "hyperoxia" can indeed provoke vasoconstriction in the feto–placental circulation.

Possibly the most informative pointer to answer these questions is contained in a report by Ramanathan [14] of the consequences of providing different concentrations of oxygen to mothers undergoing elective Caesarean section under extradural analgesia. Fetal oxygenation was found to correlate significantly with maternal Pa_{O_2}, possibly confirming reports, as discussed by Norris and Dewan [15], that materno–fetal oxygen equilibration is reached within less than 6 min. Ramanathan and colleagues also reported that "hyperoxic" fetuses were less acidotic than were "normoxic" ones.

As with the majority of studies of placental transfer, the baseline investigation must be confined to cases of elective section which satisfy the criteria of the "clinically acceptable ideal case" [16]. Studies of groups of patients with and without pathology possibly indicative of placental dysfunction, and of elective and emergency procedures, render untenable any conclusions of fetal well-being drawn from the results. The mother should not have been exposed to aorto–caval compression, either during her journey to the anaesthetic room or on the operating table. The anaesthetic technique should be standardized, the only variable being the ratio of flow rates of oxygen and nitrous oxide (it would be as well to study the three advocated concentrations of oxygen— 50, 67 and 100%). Maternal normocapnia should be maintained. In each case, the U–D interval should be within an acceptable range (up to 90 s) for this type of investigation. Traditionally—and I believe correctly—analysis of umbilical artery rather than umbilical vein blood has been quoted as indicative of the acid–base and respiratory gas status of the neonate. The Apgar-minus-colour scores at 1 and 5 min and the time to sustained respiration of the infant should be assessed (and recorded in detail) by a paediatrician known to be competent and reliable in the exercise.

A definitive investigation such as this has yet to be reported. Once the results of such a study are known and validated, consideration may then be given to the situation of the potentially less than "ideal" infant, in regard to whom it must be remembered that, owing to the characteristics of the fetal oxyhaemoglobin dissociation curve, a small increase in fetal Pa_{O_2} causes a significant increase in oxygen saturation, thus improving fetal oxygen stores preparatory to the interval between the process of delivery and the initiation of active resuscitation.

However, extrapolation of the results of a study as outlined, to the conduct of cases characterized by fetal distress, will pose many more problems. The abolition merely of uterine contractions by the general anaesthetic probably contributes to the unexpectedly healthy state of the infant frequently seen in such circumstances (an aspect of "fetal resuscitation"). If the intra-uterine distress results from massive abruption or from a severely constricted umbilical cord, with consequent gross disturbance of fetal haemodynamics, varying the concentration of maternally-inspired oxygen concentration is unlikely to make a discernible difference to the umbilical artery acid–base and respiratory gas values. Thus a very large series of subjects, grouped with meticulous care, would be required to investigate this question.

J. Selwyn Crawford

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MATERNAL INSPIRED OXYGEN CONCENTRATION AND NEONATAL STATUS FOR CAESAREAN SECTION UNDER GENERAL ANAESTHESIA

Comparison of Effects of 33% or 50% Oxygen in Nitrous Oxide

E. G. LAWES, B. NEWMAN, M. J. CAMPBELL, M. IRWIN, S. DOLENSKA AND T. A. THOMAS

SUMMARY

The relationship between maternal $F_{I_{O_2}}$ *and umbilical venous* P_{O_2}, P_{CO_2}, *pH and neonatal Apgar and TSR (time to sustained respiration) scores was studied in 35 patients undergoing Caesarean section under general anaesthesia. Patients were allocated randomly to breathe an* $F_{I_{O_2}}$ *of either 0.5 or 0.33. Umbilical venous blood was collected at the time of delivery, and TSR and 1- and 5-min Apgar scores recorded. Mean values for umbilical venous blood were:* P_{O_2} *3.9 kPa and 3.7 kPa;* P_{CO_2} *6.2 kPa and 6.2 kPa; pH 7.30 and 7.31 (50% and 33% groups, respectively* ($P > 0.05$)*). No differences were found between groups for 1- or 5-min Apgar scores or TSR values. It is concluded that no difference in fetal outcome or acid–base status can be detected when maternal* $F_{I_{O_2}}$ *is decreased from 0.5 to 0.33, and that the use of 33% oxygen in 66% nitrous oxide appears to be safe for neonates who have not suffered fetal distress before delivery.*

The conflicting requirements of adequate oxygenation and minimal drug-induced depression of the fetus at delivery, and the avoidance of intraoperative maternal awareness present a dilemma in devising an ideal general anaesthetic technique for Caesarean section. The use of an inspired anaesthetic gas mixture of 50% nitrous oxide in oxygen [1–4], with the addition of low concentrations of volatile agents represents current practice. However, this technique has not eliminated entirely the problem of awareness during operation [5].

This study was designed to compare the biochemical and physical status of neonates born to mothers given one of two commonly used ratios of nitrous oxide and oxygen to breathe during Caesarean section under general anaesthesia.

PATIENTS AND METHODS

Women included in this study, which was approved by the Bristol and Weston DHA Ethics Committee were ASA grades I or II undergoing general anaesthesia for Caesarean section. Patients were excluded from the study if there was fetal distress requiring urgent delivery. Preparation of all patients included premedication with either ranitidine 50 mg i.v. 1 h before induction, or ranitidine 150 mg by mouth 12 h and 1 h before surgery, depending on the indication for Caesarean section. After ingesting 30 ml of sodium citrate 0.3 mol litre^{-1} solution, the patient was transported to the operating theatre in the left lateral position. A 16-gauge i.v. cannula was inserted into a vein under local anaesthesia and Hartmann's solution 500–750 ml administered i.v. with the patient in the left wedged position. Baseline pre-induction arterial pressure and heart rate were recorded using an automatic non-invasive monitoring device. Pre-oxygenation was

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This article accompanies the Editorial.

E. G. LAWES,* M.B., B.S., F.F.A.R.C.S.; B. NEWMAN, M.B., CH.B., F.F.A.R.C.S.; M. J. CAMPBELL, B.A., PH.D.; M. IRWIN, M.B., CH.B., DIP.OBST.; S. DOLENSKA, L.M.S.S.A., M.D.; T. A. THOMAS, M.B., CH.B., F.F.A.R.C.S.; Sir Humphry Davy, Department of Anaesthetics, Bristol Royal Infirmary, Bristol. Accepted for Publication: April 11, 1988.

*Present address, for correspondence: Shackleton Department of Anaesthetics, Southampton General Hospital, Southampton SO9 4XY.

TABLE I. *Comparison of outcome variables for 50 % and 33 % oxygen concentration groups*

	Group A 50 % oxygen ($n = 16$)	Group B 33 % oxygen ($n = 19$)	Statistics	A − B	95 % CI for diff.
Umbilical vein					
Mean $P\text{O}_2$ (kPa)	3.9	3.7	$t = 0.6$, $P = 0.5$	1.5	−3.3–6.1
Mean $P\text{CO}_2$ (kPa)	6.2	6.2	$t = -0.1$, $P = 0.9$	−0.2	−5.3–4.8
Mean pH	7.30	7.31	$t = -0.9$, $P = 0.4$	−0.01	−0.05–2.02
Time to spontaneous ventilation (s)					
Median	12.5	10.0	$w = 2.09$, $P = 0.5$	2.5	−5–90
Range	5–180	2–240			
Apgar (minus colour): No. with scores 7 or 8					
1 min	7 (43 %)	9 (47 %)	$\chi^2 = 0.02$, $P = 0.9$	−4%	−37–29 %
5 min	16 (100 %)	17 (89 %)	—		—
Induction–Delivery interval (min)					
Median	7.0	8.0	$w = 274$, $P = 0.7$	−1.0	−3.0–1.7
Range	5–12	2–20			
Uterine incision–delivery interval (s)					
Median	80.0	87.0	$w = 270$, $P = 0.6$	−7	−45–30
Range	15–240	30–480			

undertaken using a Magill anaesthetic system with oxygen 8 litre min^{-1} for 5 min.

General anaesthesia was induced with a sleep dose of thiopentone 3–4 mg kg^{-1} i.v. and the trachea intubated, following the i.v. administration of suxamethonium 100 mg, while cricoid pressure was applied. Neuromuscular blockade was provided with atracurium 0.3 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide and 0.8 % isoflurane in oxygen. The patient's lungs were ventilated with a non-rebreathing circuit, a minute volume dividing ventilator and a tidal volume of 10 ml kg^{-1} and frequency of 12 b.p.m. in order to avoid hypocapnia. Maternal arterial pressure, ECG and heart rate were monitored and measurements recorded at regular intervals.

Patients were allocated alternatively to receive oxygen and nitrous oxide in either a 50:50 ratio (group A) or a 33:67 ratio (group B). The two anaesthetic techniques were otherwise identical. The oxygen concentration of the inspired gas was measured using an oxygen analyser and the total fresh gas flow monitored with a Wright's spirometer.

At delivery of the infant, a segment of cord was double cross clamped immediately and blood samples obtained from the isolated vein into heparinized syringes. The samples were placed on ice and analysed within 30 min using an automated machine that was calibrated regularly. Umbilical vein oxygen tension, carbon dioxide tension and pH were measured.

The following data relevant to neonatal outcome were collected: presentation of the infant at birth, induction to delivery interval (min), uterine incision to delivery interval (s) and time to sustained ventilation (s). Neonatal Apgar scores at 1 and 5 min were awarded on a scale of 1–8 (excluding colour) by paediatricians who were unaware of the maternal inspired oxygen concentration.

At the postoperative visit, recollection of intraoperative dreams and the possibility of awareness were sought.

Student's t test was used to compare the two groups for data that were distributed normally (umbilical vein $P\text{O}_2$, $P\text{CO}_2$ and pH). For time to spontaneous ventilation, induction to delivery interval (I–D) and uterine incision to delivery (U–D) interval, the Mann–Whitney U test was used. Apgar scores were compared using a Chi-squared test with Yates' correction.

RESULTS

Thirty-five patients were included in the study: 16 in group A (50 % oxygen) and 19 in group B (33 % oxygen). Indications for Caesarean section included breech presentation, previous Caesarean section, cephalo–pelvic disproportion and failure to progress in labour.

There were no statistically significant differences between the two groups with regard to outcome variables (table I). The condition of the neonates at birth was generally good. The two neonates in group B with 5-min Apgar scores less than 7 both had scores of 6. In the first infant the individual umbilical vein P_{O_2} was 3.5 kPa, but the I–D time was 120 s—a time associated with peak circulating concentrations of thiopentone. In the second infant no cause for the score to be 6/8 was identifiable.

Factors likely to influence neonatal outcome, other than the choice of anaesthetic technique, were noted. By chance, all of the abnormal presentations at delivery occurred in the group which received 33 % oxygen: all neonates in group A were delivered head first and there were four breech presentations and one transverse lie in group B. No apparent differences were demonstrated between the condition of the neonates born to each group. There was no episode of hypotension in any patient defined as a systolic arterial pressure of less than 100 mm Hg or a reduction in systolic pressure of 30 mm Hg during the induction–delivery interval. At postoperative interview, some mothers reported pleasant dreams, which bore no relationship to the anaesthetic or surgery. There were no reports of awareness under anaesthesia.

DISCUSSION

The techniques of general anaesthesia for Caesarean section are designed to optimize neonatal condition at delivery, produce maternal cardiovascular stability and prevent maternal pulmonary aspiration. They may result in an appreciable and probably under-reported incidence of intraoperative awareness because of inadequate depth of anaesthesia. This problem has been discussed widely [6–15]. Some have suggested that a brief and mild degree of neonatal sedation following delivery, caused by the use of higher concentrations of volatile agents, represents a minor disadvantage for reducing the incidence of intraoperative awareness [5, 16]. However, this approach carries the increased risk of inducing maternal hypotension and inhibiting uterine contraction after delivery, resulting in haemorrhage [3].

In clinically appropriate concentrations, nitrous oxide does not inhibit uterine contraction, and higher concentrations are associated with deeper planes of anaesthesia, particularly in pregnancy [17]. Furthermore, increasing the $F_{I_{N_2O}}$ increases the rate of uptake of volatile anaesthetic agents by the second gas affects, thereby hastening the onset of surgical anaesthesia.

A number of studies have been undertaken in the past to investigate the influence of different $F_{I_{O_2}}$ values on neonatal outcome. However, none has been undertaken to compare an $F_{I_{O_2}}$ of 0.33 with 0.5.

Our data suggest that there is no difference in neonatal outcome if the maternal $F_{I_{O_2}}$ is decreased from 0.5 to 0.33. Our results differ from similar work in a number of important respects. The most widely quoted publication on varying maternal inspired oxygen concentrations and neonatal condition at delivery by Caesarean section is by Marx and Mateo [4]. They reported that an increased maternal $F_{I_{O_2}}$ was associated with increased umbilical venous oxygen tensions. The $F_{I_{O_2}}$ favoured most was 0.6. They reported that a higher umbilical venous oxygen tension was associated with improved clinical condition of the infant at 1 min. However, no difference in neonatal outcome persisted for more than 5 min after delivery, suggesting that any differences at 1 min resulted from temporary sedation by rapidly excreted anaesthetic agents.

The study by Rorke [1] also failed to present biochemical data as evidence that the low Apgar scores obtained in the low (33 %) oxygen group neonates resulted from asphyxia. Despite the long I–D intervals (45.9–52.3 min) and the resultant increase in nitrous oxide received by the neonate that this would induce, the physical findings of apnoea, cyanosis, bradycardia and hypotonus implicit in an Apgar score of 3 do not reflect the known pharmacological properties of nitrous oxide in the neonate.

There is no evidence that the umbilical venous P_{O_2} produced with a maternal $F_{I_{O_2}}$ of less than 0.5 is pathological and not tolerated easily by the neonate. In all the studies in which umbilical venous P_{O_2} has been measured, the values presented are in excess of those obtained at normal vertex delivery. In the low oxygen group (28 %) in the study by Marx and Mateo [4], the umbilical vein P_{O_2} of the neonates was 3.7 ± 0.3 kPa, similar to that found in normal vertex delivery. Mean umbilical vein oxygen tensions at normal vertex vaginal delivery reported in various studies lie in the range 2.8–3.9 kPa [21]. Analysis of the umbilical vein pH in all groups failed to demonstrate evidence of fetal asphyxia in any neonate, irrespective of the maternal $F\text{I}_{O_2}$ [1].

It has been suggested that maintaining a high maternal $F\text{I}_{O_2}$ ensures adequate oxygen reserves in the neonate after delivery [4]. However, values of maternal $F\text{I}_{O_2}$ greater than 0.5 are required if significant increases in umbilical vein $P\text{O}_2$ are needed. It is our view that the theoretical advantage of achieving neonatal oxygen tensions greater than those found at normal vertex vaginal delivery is of doubtful value, particularly if this is at the expense of adequate maternal anaesthesia.

Induction–delivery intervals of 7–8 min imply that equilibration between inspired concentrations of nitrous oxide and volatile agents does not occur [18]. Materno–fetal equilibration of nitrous oxide takes 35 min or more after an initial rapid uptake by the fetus [18, 19]. Nitrous oxide taken up by the fetus *in utero* is excreted rapidly within a few breaths by the neonate [20].

Although Marx and Mateo used prophylactic uterine displacement to prevent aortocaval compression and obtained I–D and U–D intervals similar to those of the present study, their results cannot be compared directly with ours. Their choice of volatile anaesthetic agents differed for each oxygen group, thus introducing a variable other than $F\text{I}_{O_2}$. Thus there is a possibility that the volatile anaesthetic agent may have a more significant effect on the neonate and utero–placental perfusion than was realized. These authors also reported that significantly higher Apgar scores were obtained in neonates born to hyperoxygenated mothers. This difference was based on a single 1-min score. Comparison of the first of two Apgar scores with a second is a more useful indicator of neonatal well-being than a single score. The use of two scores at a 5-min interval enables temporary sedation, evident within 1–2 min of birth and induced by rapidly excreted inhalation anaesthetic agents, to be distinguished from the consequences of intra-uterine asphyxia. Oliver, Demis and Bates [22] found no differences after 5 min from birth between the neonates whose mothers had received oxygen continuously before delivery and those that had not.

Other studies [1, 2] have supported the finding of a positive correlation between maternal inspired oxygen concentrations and umbilical oxygen tensions, although the anaesthetic techniques used differed considerably from current practice. No lateral tilt or wedge was used by these investigators. Moir [3] compared the effects of two concentrations of nitrous oxide, but only one group received a volatile agent. Rorke [1] and his fellow authors were also unaware of the significance of prolonged I–D and U–D intervals. The latter value extended to 45 min or more in some patients.

Ramanathan and colleagues [23] have demonstrated that maternal hyperoxia increases umbilical venous and arterial $P\text{O}_2$ values and acid–base status during Caesarean section under extradural anaesthesia. These authors suggested that improvement in the neonate occurred because the umbilical venous $P\text{O}_2$ was increased, although they were unable to demonstrate any significant difference in 1- and 5-min Apgar scores. Both the umbilical venous and umbilical arterial values reported were equal or in excess of the umbilical venous $P\text{O}_2$ found at normal vertex delivery, even with an $F\text{I}_{O_2}$ of 0.21. It is a matter of debate if this represents an improvement.

In conclusion, our results show that, during general anaesthesia for Caesarean section, reduction of the $F\text{I}_{O_2}$ from 50 % to 33 % in nitrous oxide with 0.8 % isoflurane is not associated with a clinically or statistically significant difference in the biochemical or clinical status of the neonates born within approximately 7–8 min of induction of anaesthesia. It is our view that an increased concentration of nitrous oxide can be used without detriment to the neonate in the absence of severe fetal distress. Although the study was not designed to investigate the incidence of maternal awareness during general anaesthesia for Caesarean section, theoretically this technique should reduce the incidence further.

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MAXIMUM FI_{O_2} DURING CAESAREAN SECTION

D. G. BOGOD, M. ROSEN AND G. A. D. REES

SUMMARY

Forty patients undergoing elective and emergency Caesarean section (excluding severe fetal distress) were divided into four groups to receive 50% oxygen, 50% nitrous oxide, and 0.5% halothane (group 1, controls) or 100% oxygen supplemented by 1.5 × MAC of halothane, enflurane or isoflurane (groups 2, 3, 4, respectively) reducing to 1.0 × MAC 5 min after induction. The umbilical venous PO_2 in the oxygen-only groups was higher than in the oxygen–nitrous oxide groups, this difference reaching statistical significance when the patients in the oxygen-only groups were combined. Blood loss and uterine contractility were unaffected by the increased concentrations of volatile agents, and awareness did not occur. Improved cardiovascular stability was demonstrated in the elective high-oxygen groups. The technique is safe and warrants further study, since there are no important ethical objections.

Moir [1] first proposed 50% oxygen, 50% nitrous oxide and 0.5% halothane as a method for maintaining anaesthesia for Caesarean section, since when it has become the standard technique in the U.K.

The wide acceptance of an inspired oxygen concentration (FI_{O_2}) of 0.5 is largely based upon three frequently-quoted studies which investigated the effect of increasing inspired oxygen concentration (FI_{O_2}) upon fetal oxygenation as measured by umbilical vein partial pressure of oxygen (Puv_{O_2}) [2–4]. These studies showed a "ceiling" effect, whereby any increase in the maternal arterial PO_2 above 40 kPa failed to produce a corresponding increase in Puv_{O_2}. This "optimum" PO_2 corresponded to an FI_{O_2} between 0.5 and 0.65. Rorke, Davey and DuToit [2] even suggested that a decrease in fetal PO_2 occurred when maternal oxygen tension exceeded this value.

An important criticism of these studies is that the concentration of anaesthetic agents administered—especially in the mothers receiving an FI_{O_2} of near 1.0—may have been inadequate to ensure unconsciousness. Although no attempt was made to assess awareness in these trials, it is conceivable that there could have been high circulating catecholamine concentrations—which would reduce intervillous blood flow and adversely affect placental gas exchange [5–7]. In the studies by Baraka [3] and by Rorke, Davey and DuToit [2], this effect would certainly be potentiated by aorto–caval compression, the prevention of which was not widespread then, and which is not referred to by the authors.

The present study was designed to compare the effects of increasing FI_{O_2} upon fetal oxygenation, at a comparable depth of anaesthesia. For this to be possible, higher than usual inspired concentrations of volatile agents are required, and the effect of these upon blood loss and uterine contractility should be monitored. It was also proposed to determine awareness, questioning patients as well about dreams or other manifestations of inadequate depth of anaesthesia.

PATIENTS AND METHODS

Details of the trial were approved by the Ethics Committee of the Divisions of Anaesthesia and Obstetrics. It was decided that the trial on elective Caesarean section should be completed satisfactorily before patients having emergency Caesarean section were studied.

Patients undergoing elective (and subsequently

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emergency) Caesarean section under general anaesthesia were selected and allocated from a computer-generated randomized table to one of four groups as follows:

Group 1: 50% oxygen–50% nitrous oxide + 0.5% halothane (controls).
Group 2: 100% oxygen + 1.1% halothane for 5 min, 0.75% halothane thereafter.
Group 3: 100% oxygen + 2.5% enflurane for 5 min, 1.7% enflurane thereafter.
Group 4: 100% oxygen + 1.8% isoflurane for 5 min, 1.2% isoflurane thereafter.

Patients with diabetes, severe pre-eclampsia, multiple pregnancy or who were less than 36 weeks pregnant were excluded. Each patient gave informed consent after an explanation.

Magnesium trisilicate (BP) 30 ml was administered immediately before the patient was transferred to the operating theatre. The mother was placed in the left lateral position breathing 30–40% oxygen through a Hudson mask during transfer. No premedication was given. A 14-gauge Venflon cannula was sited in a large vein on the non-dominant forearm for an infusion of Hartmann's solution. The cuff of a Dinamap automatic arterial pressure monitor was applied to the upper arm, and a standard sphygmomanometer cuff to the same forearm. A few early patients had a 22-gauge Venflon cannula inserted, under local anaesthesia, into the radial artery of the non-dominant hand which was connected via a pressure transducer and pre-amplifier to a chart recorder.

The patient was placed on the operating table in left lateral tilt of approximately 15° and the oxygen mask exchanged for a Magill system, through which she breathed 100% oxygen 8 litre min^{-1}. During this time, a preoperative measurement of arterial pressure was obtained (Dinamap or direct). After 3 min, cricoid pressure was applied and the forearm tourniquet inflated to 50% above systolic arterial pressure and clamped, to isolate the hand from the effects of the neuromuscular blocking drugs. Thiopentone 3–4 mg kg^{-1} was administered, followed by suxamethonium 1.5 mg kg^{-1}.

After intubation of the trachea, pancuronium 0.1 mg kg^{-1} was administered and mechanical ventilation instituted (Manley). A Datex Normocap carbon dioxide monitor was attached to the tracheal tube. Ventilation of the lungs was with different gas mixtures, using vaporizers previously calibrated with a Datex Normac anaesthetic agents monitor, according to previously determined random group allocation.

The chosen regimen was continued until the baby had been delivered and the cord clamped, at which time the mixture was switched to 30% oxygen–70% nitrous oxide, and an opioid drug administered. After delivery, syntocinon 10 u. was administered i.v.

Measurements

Arterial pressure was measured every 1 min (Dinamap). The hand isolated from neuromuscular blockade was observed and, when movements were seen, the concentration of volatile agent was increased by 50% until movement stopped. Fresh gas flow was adjusted to maintain the end-expiratory carbon dioxide partial pressure at 4 kPa. In patients with an arterial cannula, arterial blood samples for gas analysis were taken at the beginning and end of the pre-oxygenation period, and immediately before delivery.

After delivery the obstetrician, who was unaware which technique had been used, was asked to assess the contractile state of the uterus by palpation, expressing the score on a 1–4 scale, repeated just before closure of the visceral peritoneum.

Heparinized blood samples were obtained from the umbilical artery and veins for gas analysis (taken from a clamped section of umbilical cord). The neonate was assessed by a paediatrician unaware of the anaesthetic technique. Apgar scores at 1 and 5 min, the times to first breath and sustained respiration, and required resuscitation were recorded.

Blood loss was estimated by weighing swabs and adding the contents of the suction bottle and an estimate for blood spilt on towels and floor. Samples for haemoglobin estimation were taken before, and at 24 and 48 h after, surgery. At these times mothers were questioned about awareness and dreaming.

Extension of the trial

Following satisfactory results in the elective group, the study was resubmitted to the Ethics Committee, and the trial extended to patients undergoing emergency Caesarean section, but excluding any with severe fetal distress. Patients were randomly allocated, having given consent following an appropriate explanation. Treatment and follow-up was similar to that received by

TABLE I. *Demographic data—mothers. †Some patients had multiple indications*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Weight (kg) (mean (SD))	67.0 (8.9)	75.0 (12.2)	66.4 (10.9)	65.2 (8.1)	70.2 (11.6)	62.4 (9.5)	67.2 (9.5)	64.8 (10.7)
Parity								
Primiparous	1	0	1	1	5	2	2	0
Multiparous	4	5	4	4	0	3	3	5
Indication for Caesarean section†								
Previous C.S.	4	3	3	3	0	1	2	5
Abnormal lie	2	2	3	0	0	2	1	0
Cephalo-pelvic disproportion	1	1	0	0	0	0	0	0
Fetal distress	0	0	0	0	2	4	1	2
Failure to progress	0	0	0	0	5	2	4	3
Other	1	1	1	3	0	1	0	0

elective cases. Arterial cannulation was not performed on any of these patients.

Statistics

Continuously variable data were analysed by Dunnett's test for comparing multiple groups with a control or the Kruskal-Wallis one-way analysis of variance by ranks, depending upon the normality of the distribution. Ordinal data were analysed using the chi-squared or Fisher exact test where appropriate. Values of P lower than 0.05 were taken as statistically significant.

RESULTS

Forty patients were studied in all, five in each emergency and elective group. The patients were similar with respect to weight, parity and indications for Caesarean section (table I). As might be expected, a higher proportion of emergency cases were primiparous patients.

Eight patients (two from each elective group) had an arterial cannula inserted before induction. With the patient breathing approximately 30% oxygen, the mean difference between alveolar and arterial oxygen partial pressures($P_{A_{O_2}} - P_{a_{O_2}}$) was 4.1 kPa in the control patients (group I) and 7.9 kPa in the high-oxygen patients (groups 2, 3 and 4) (ns). Following pre-oxygenation with 100% oxygen, the alveolar-arterial gradients were 37.5 kPa and 39.3 kPa, respectively. At delivery, control patients had a gradient of 18.3 kPa, compared with 41.2 kPa in the high-oxygen groups, this larger gradient being consistent with the greater $F_{I_{O_2}}$. Following these results, it was felt unnecessary to continue the practice of arterial cannulation in order to verify these effects.

Blood loss

The mean blood loss was estimated as less than 1 litre in each group (table II). In elective patients, only those receiving 100% oxygen and enflurane (group 3), lost more blood than patients having oxygen and nitrous oxide (group 1) (874 ml *v.* 619 ml ($0.05 < P < 0.01$)). This was not found in emergency patients, in whom all three increased oxygen groups (2, 3 and 4) had a non-significant but lower blood loss than the controls (group 1).

The lower of the haemoglobin estimates at 24 and 48 h after surgery was compared with the preoperative values, and the percentage values, and the percentage change calculated. In elective operations, one patient in group 3 had been given a postoperative blood transfusion, as had two in emergency group 4. In these patients, the immediate pretransfusion haemoglobin concentration was used to assess the decrease in haemoglobin value. One patient in the emergency group 1 needed intraoperative transfusion (the placenta was incised), and this patient was excluded from the analysis. It can be seen that the decrease in haemoglobin concentration was consistently greater in emergency than in elective patients, despite similar estimates of blood loss. In the

TABLE II. *Blood loss, uterine contractility and change in haemoglobin over 48 h. *$0.05 < P < 0.1$ compared with group 1*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Blood loss (ml) (mean (SD))	619 (87)	689 (197)	874* (317)	613 (205)	896 (559)	740 (191)	610 (270)	641 (145)
Uterine contractility								
1st assessment								
None/poor	1	0	0	1	1	2	1	2
Moderate/good	4	5	5	4	4	3	4	3
2nd assessment								
None/poor	1	0	0	0	0	0	1	0
Moderate/good	4	5	5	5	5	5	4	5
Maximum decrease in Hb (%) (mean (SD))	5.5 (2.8)	7.4 (5.3)	8.3 (5.6)	11.4* (4.8)	13.1 (5.3)	21.4 (10.3)	12.8 (7.5)	15.6 (7.2)

TABLE III. *Arm movement and awareness*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Isolated arm								
Movement	0	1	1	1	1	1	1	0
No movement	5	4	4	4	4	4	4	5
Awareness								
Dreaming	0	0	1	0	0	0	0	0
No dreaming	5	5	4	5	5	5	5	5

elective patients, group 4 (isoflurane) had a greater decrease in haemoglobin concentration than the control group (11.4% *v.* 5.5% ($0.05 < P < 0.1$)).

Uterine contractility (table II)

Uterine contractility as assessed by the obstetrician showed that all but two elective patients had a moderately or well-contracted uterus at first assessment; in only one patient (in the control group) was poor contractility still present by the second assessment. In the emergency groups, six patients had a flaccid or poorly contracted uterus at first assessment, but five were moderately or well contracted by the second assessment. There were no important differences between any group.

Arm movement and awareness (table III)

In both elective and emergency groups, three patients (15%) demonstrated spontaneous clenching movements of the isolated hand. In these patients the inspired concentration of the volatile agent was increased by 50% until movements ceased. No patient reported recollection at postoperative interview. Only one patient (elective group 2) reported dreaming—a sensation of floating during the anaesthetic; she had no recollection of specific incidents or of any pain and was untroubled by the experience.

Arterial pressure (fig. 1)

For each mother, the highest and lowest mean arterial pressures, as recorded by the Dinamap, are displayed as percentage change from the preoperative value. Recording was taken from 3 min after intubation to minimize effects from the hypertensive influence of laryngoscopy. No mother had a mean change in arterial pressure of more than +52% or −34% compared with the preoperative value. If the median is taken for each

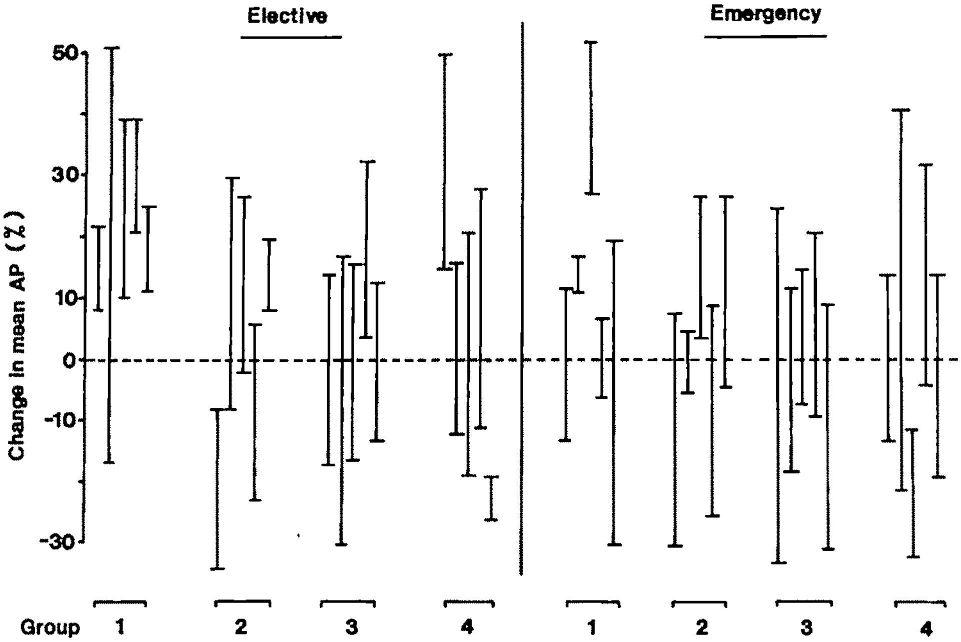

FIG. 1. Range of mean arterial pressures for each patient (% change from preoperative values).

TABLE IV. *Demographic data—babies.* †*There were no babies of 36–38 weeks gestation*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Weight (kg) (mean (SD))	3.19 (0.60)	3.45 (0.70)	3.48 (0.41)	3.18 (0.45)	3.89 (0.58)	3.13 (1.04)	3.01 (0.65)	3.50 (0.36)
Estimated maturity (weeks)†								
< 36	0	1	0	0	0	1	1	0
38–40	5	4	5	5	4	4	4	5
> 40	0	0	0	0	1	0	0	0

patient as a measure of the cardiovascular stability of the anaesthetic used, then elective patients receiving enflurane (group 3) were significantly more stable than the control group (mean 2.1 % *v.* 20.8 % ($P < 0.05$)). The other two trial groups also appeared more stable than the controls (ns). There was no difference between patients undergoing emergency procedures.

The baby (table IV)

The mean weight of the babies in the emergency enflurane group was lower than other groups (ns). One patient in emergency group 2 (halothane) underwent Caesarean section at 33 weeks gestation for intrauterine growth retardation and fetal distress, delivering a baby of birth weight 1.18 kg. Since this patient would be expected to have significant feto–placental dysfunction, that baby's data were excluded.

Umbilical vein blood-gas tensions (table V)

The mean umbilical vein P_{O_2} was greater when the volatile agent was supplemented by oxygen alone, in both elective and emergency patients. In elective patients mean P_{O_2} in groups 3 and 4 was 5.8 kPa and 5.7 kPa, respectively, compared with

TABLE V. *Umbilical vein blood-gas tensions (mean (SD)).* $^*P < 0.05$; $†0.05 < P < 0.01$, *compared with group 1*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
$P\mathrm{o}_2$ (kPa)	4.5	5.3	5.8†	5.7†	4.9	5.2	5.4	5.8†
	(0.9)	(0.7)	(1.2)	(1.1)	(1.0)	(1.2)	(0.7)	(0.5)
$P\mathrm{co}_2$ (kPa)	6.0	5.5	5.7	5.8	5.7	6.4	5.9	5.8
	(0.4)	(0.5)	(0.6)	(0.6)	(0.6)	(0.6)	(0.5)	(0.5)
pH	7.35	7.34	7.35	7.36	7.33	7.28	7.33	7.36
	(0.02)	(0.03)	(0.02)	(0.02)	(0.03)	(0.04)	(0.25)	(1.15)
Base deficit	0.94	3.84*	1.66	1.18	3.14	4.55	2.34	1.08
(mmol litre^{-1})	(0.76)	(1.27)	(0.70)	(1.14)	(2.21)	(0.36)	(2.54)	(0.84)

TABLE VI. *Umbilical artery blood-gas tensions (mean (SD)).* $^*P < 0.05$ *compared with group 1*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
$P\mathrm{o}_2$ (kPa)	2.7	3.4	3.1	2.5	2.7	3.0	2.7	3.3
	(0.7)	(1.0)	(0.7)	(0.7)	(0.7)	(0.5)	(0.4)	(0.6)
$P\mathrm{co}_2$ (kPa)	6.4	5.6	6.7	6.7	7.0	7.0	6.3	6.2
	(0.5)	(0.6)	(0.5)	(1.2)	(0.6)	(0.3)	(1.2)	(1.4)
pH	7.32	7.32	7.31	7.31	7.29	7.22	7.29	7.33
	(0.03)	(0.02)	(0.02)	(0.02)	(0.03)	(0.07)	(0.04)	(0.04)
Base deficit	1.64	4.68*	1.62	2.10	2.64	7.00	5.34	1.52
(mmol litre^{-1})	(0.45)	(0.65)	(0.54)	(2.36)	(1.61)	(4.70)	(2.03)	(1.65)

TABLE VII. *Neonatal data*

	Elective				Emergency			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Apgar score								
1 min								
0–3	0	0	0	0	1	1	1	0
4–7	1	0	0	0	1	1	0	1
8–10	4	5	5	5	3	2	4	4
5 min								
0–3	0	0	0	0	1	0	0	0
4–7	0	0	1	0	0	1	0	0
8–10	5	5	4	5	4	3	5	5
Time to sustained respiration								
< 1 min	4	4	4	5	2	4	4	4
> 1 min	1	1	1	0	3	1	1	1
Resuscitation								
Suction only	2	2	3	3	1	2	3	3
+ oxygen	2	2	1	2	1	2	3	3
+ IPPV	1	1	1	0	1	0	0	2
+ intubation	0	0	0	0	1	1	1	0

4.5 kPa in the control group ($0.05 < P < 0.1$). In emergency patients, mean $P\text{o}_2$ in group 4 was 5.8 kPa, compared with 4.9 kPa in the control group ($0.05 < P < 0.1$). When the groups were combined and all patients receiving oxygen alone were compared with all those receiving oxygen–nitrous oxide, the mean umbilical vein $P\text{o}_2$ was significantly greater in the former group (5.6 kPa *v.* 4.7 kPa ($0.01 < P < 0.05$)). There was no significant difference in $P\text{co}_2$ or pH between any group. The mean base deficit of elective group 2 (halothane) was 3.84 mmol litre^{-1}, compared with 0.94 mmol litre^{-1} in the control group (1) ($P < 0.05$). There were no other significant differences between groups.

Umbilical artery blood-gas tensions (table VI)

The mean oxygen tensions were consistently lower than venous samples. There was no significant difference with respect to $P\text{o}_2$, $P\text{co}_2$ or pH between groups. Elective group 2 showed a significantly higher base deficit than the control group (4.78 *v.* 1.64 ($P < 0.05$)).

Apgar scores, respiration and resuscitation (table VII)

The Apgar scores at 1 and 5 min were lower in the babies born by emergency Caesarean section. There were no significant differences between groups. The time to sustained respiration did not differ significantly between groups, although only one neonate (20%) in each of the high oxygen groups of emergency patients took longer than 1 min to achieve sustained respiration, compared with three (60%) in the control group. There were no differences between resuscitation required for the neonates.

DISCUSSION

The standard anaesthetic technique for Caesarean section is 50% oxygen, 50% nitrous oxide and 0.5% halothane which provides 1.2 × MAC when both nitrous oxide and halothane are considered. In previous investigations into high inspired oxygen concentrations, multiples of MAC well below 1.0 were administered to several of the trial groups. Thus only 20% of the patients of Marx and Mateo [4] received an anaesthetic which provided greater than 1.0 × MAC. The other patients had multiples of MAC between 0.52 and 0.62. Moir [1] described a 4% incidence of recollection of painful incidents in Caesarean section in patients anaesthetized with 70% nitrous oxide and 30% oxygen, which provides 0.64 × MAC. Baraka [3] administered anaesthetics providing multiples of MAC between 0.48 and 0.76. Rorke, Davey and DuToit [2] used ether or methoxyflurane to achieve multiples of MAC greater than 1.0, but the high blood-gas solubility of these agents suggests that they would be ineffective over a short period of time between induction and delivery. It is possible that high circulating concentrations of catecholamines played a part in limiting fetal oxygen transfer by causing uterine artery vasoconstriction and reducing intervillous blood flow.

In patients having oxygen and a volatile agent only, inspired concentrations were standardized to provide 1.5 × MAC, reducing to 1.0 × MAC after 5 min. The high initial inspired concentration of volatile agent was used to provide "overpressure" to compensate for the loss of rapid onset of effect of nitrous oxide, and of the second-gas effect.

High alveolar–arterial $P\text{o}_2$ differences were found before and after preoxygenation in the mothers in whom arterial cannulation was performed. These correspond closely to the findings of Jassir, Yu and Marx [8] who investigated ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) in mothers at full term using different methods of uterine displacement, and can be explained by the increased ventilation–perfusion mismatch as a result of diaphragmatic splinting. The alveolar–arterial difference was further increased following a period of intermittent positive pressure ventilation with near-100% oxygen; this is indicative of further ventilation–perfusion mismatch, and is to be expected in mechanically ventilated subjects.

In contrast to earlier studies, the results of the present trial suggest that the cord venous $P\text{o}_2$ is greater in babies whose mothers receive 100% oxygen. The differences between mean values were not significant at the 5% level, but this is not surprising when considering the wide variation between individuals and the very small numbers in each group. Although the changes in $P\text{o}_2$ result in only a small increase in fetal oxygen content, the benefit might be far greater in a fetus suffering from intrauterine asphyxia as a result of severe pre-eclampsia, abruption or ante-partum haemorrhage; such patients were excluded for ethical reasons. Furthermore, *any* increase in oxygen content would stand the fetus in good stead

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during delay in establishing spontaneous respiration.

No greater blood loss or decrease in haemoglobin concentration occurred in the trial groups than in controls, and uterine contractility was unaffected by the regimen. The duration of exposure to a volatile agent is obviously important in determining its effect upon the uterus, and accounts for lack of effect of even 1.5 % halothane at limited exposure. In any event, a rapid decrease in arterial concentration would be anticipated on discontinuing the volatile agent; thus any adverse effect upon uterine contractility would be short-lived.

Tunstall [9] described a simple technique to monitor awareness. A modified version was used as it seemed practical to look for spontaneous movement of the non-paralysed hand, and increase the delivered concentration of anaesthetic agent as necessary. No patient reported any recollection. The only patient who reported dreaming showed no movement of the isolated hand, which may be an unusual failure of the technique. No patient receiving isoflurane (group 4) reported awareness and only one (10 %) needed an increased concentration of isoflurane.

In conclusion, the use of oxygen supplemented only by a volatile agent at a delivered concentration of 1.5 × MAC, reducing to 1 MAC after 5 min, probably results in greater partial pressures of oxygen in the umbilical vein, and improved fetal oxygen delivery. This could be of benefit to a severely compromised fetus. No increase in blood loss or decrease in uterine tone was associated with this technique. There was no associated increase in incidence of awareness. Further study of the technique in larger numbers with severe fetal distress, particularly emphasizing the use of isoflurane, is justified.

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COMPLICATIONS RELATED TO ANAESTHESIA IN INFANTS AND CHILDREN

A Prospective Survey of 40240 Anaesthetics

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SUMMARY

A prospective survey of anaesthesia-related mortality and morbidity in infants and children was carried out in a representative sample of anaesthetics performed in 440 institutions chosen at random in France. A total of 40240 anaesthetics were administered to patients younger than 15 yr, 2103 (5%) involving infants (younger than 1 yr). Twenty-seven major complications related to anaesthesia occurred during or within 24 h of the anaesthesia—an incidence of 0.7 per 1000 anaesthetics. Nine, of which four were associated with cardiac arrest, were observed in infants, whereas in children there were 18 complications of which eight were associated with cardiac arrest, one with fatal outcome. The risk of complications was significantly higher ($P <$ *0.001) in infants (4.3 per 1000) than in children (0.5 per 1000). Accidents observed in infants mainly occurred during maintenance of anaesthesia and were the result of respiratory failure. In children, circulatory failure was as frequent as respiratory failure and complications were observed almost equally during induction and maintenance and on recovery. The rate of complications increased significantly with the ASA score and the number of co-existing diseases. The incidence was also higher when a previous history of anaesthesia was present, when the procedure was an emergency, and when the duration of preoperative fasting was less than 8 h.*

Epidemiological data concerning anaesthesia-related mortality and morbidity in children are few and are now largely outdated because of the many advances in the standard of anaesthetic practice [1–4]. These surveys involved teaching hospitals and gave a rough estimate of the overall risk but, since they were retrospective, did not permit the investigation of risk factors. In addition, they focused on deaths and cardiac arrests and did not include other life-threatening accidents.

Major anaesthetic complications occurring in children were assembled from a prospective survey of complications related to anaesthesia conducted in France between 1978 and 1982 and analysed. The overall rate and lethality of anaesthetic complications in children were assessed, and their causes and any attendant risk factors determined.

PATIENTS AND METHODS

Details of the methods utilized in this study have been published previously [5].

Four hundred and sixty-one institutions were chosen at random from the whole of France, including paediatric and general hospitals, and private institutions. Paediatric patients (younger than 15 yr) were admitted by 440 of them. In this prospective study, all anaesthetics, general and regional, delivered by or under the direction of certified anaesthetists, were considered, including those administered for radiological or endoscopic investigations. A questionnaire was completed by the anaesthetist for each anaesthetic.

A major complication was defined as any fatal

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or life-threatening accident or any incident producing severe sequelae, which occurred during, or within 24 h of, anaesthesia. Whether or not it appeared to be related to anaesthesia, a supplementary questionnaire was required to be completed. At the conclusion of each report, the contribution of anaesthesia to the complication was assessed, by the anaesthetist involved with the case, as "nil", "partial" or "total". All reports were then scrutinized by a National Committee of Assessors, including anaesthetists who held an academic position, which made its own assessment of the role of anaesthesia. Each case was finally assigned as "totally", "partially" or "not" related to anaesthesia—"total" when anaesthesia was the direct cause or a major contributory factor of the complication, and "partial" when the complication was primarily a result of the patient's disease or the surgical procedure, but an anaesthetic contribution could not be entirely excluded.

Complications related totally or partially to anaesthesia were classified according to the mechanism primarily responsible: failure of respiratory homeostasis, or failure of circulatory homeostasis. Within these groups, they were further subdivided according to the time of their occurrence: at induction of anaesthesia (within 10 min of the start of anaesthesia); maintenance of anaesthesia (until the end of the surgical procedure); post-anaesthetic period (up to 24 h after the end of surgery). As far as possible, complications classified were based on the cause presumed to be at the origin of the accident; for example, laryngospasm was not reported as a complication, since it was a symptom and not a cause. An exception was the group "sudden cardiac arrest", since the cause could not be established.

Risk factors studied were the patient's preoperative condition (ASA physical status, number of co-existing diseases, previous history of anaesthesia, duration of preoperative fasting), and whether the procedure was elective or emergency.

Results in infants (younger than 1 yr) were analysed separately from those of children (aged 1–14 yr), except for the study of risk factors because of the low frequency of complications. The incidence of complications in the paediatric group was compared with that in adults, assessed from the survey of Tiret and colleagues [5]. The Chi-square test was used for statistical comparison of the rates of complications in different groups. When expected frequencies were small, the exact probability was calculated.

RESULTS

During the survey, 40240 anaesthetics were administered to patients younger than 15 yr, 2103 (5%) to infants (< 1 yr). The types of procedure being undergone are summarized in table I. In the infant group, abdominal surgery was the most frequent procedure whereas, in children, ENT surgery was the most common procedure. Diagnostic investigations accounted for more than 10% of the procedures performed in infants.

Complications

In the 40240 procedures, 27 major complications related to anaesthesia occurred during or within 24 h of anaesthesia. Almost all (25) were deemed to be totally related to anaesthesia. Nine

TABLE I. *Types of procedure in infants (< 1 yr) and children (1–14 yr); percentage of total procedures* (n) *in each group*

	Infants ($n = 2103$)	Children ($n = 38137$)	Both ($n = 40240$)
ENT surgery	18.4	31.6	30.9
Abdominal surgery	28.5	25.0	25.2
Orthopaedic and trauma surgery	8.5	12.4	12.2
Male genital surgery	5.1	9.1	8.9
Diagnostic investigations	13.6	3.3	3.8
Oral surgery	1.0	3.9	3.7
Ophthalmological surgery	2.1	2.9	2.8
Urological surgery	1.6	0.9	1.0
Neurosurgery	4.3	0.5	0.7
Cardiovascular surgery	3.0	0.5	0.7
Miscellaneous	13.9	9.9	10.1

TABLE II. *Number of complications related to anaesthesia in infants (< 1 yr) and children (1–14 yr). † One death*

	Infants ($n = 2103$)	Children ($n = 38137$)	Both ($n = 40240$)
Cardiac arrest	4	8†	12
Other	5	10	15
Total	9	18	27

TABLE III *Incidence (No. per 1000) of anaesthetic complications in infants and children, compared with results in adults (ref. [5]). **P < 0.01; ***P < 0.001; ns = not significant*

	All complications	Cardiac arrests	Deaths
Infants < 1 yr	4.3	1.9	—
	***	**	ns
Children 1–14 yr	0.5	0.2	0.03
Total 0–14 yr	0.7	0.3	0.02
	***	**	***
Adults ⩾ 15 yr	1.5	0.7	0.4

of these complications were observed in infants, four associated with cardiac arrest. In children, 18 complications were observed, eight associated with cardiac arrest. One had a fatal outcome (table II).

All complications were observed in patients undergoing general anaesthesia, but it must be noted that regional anaesthesia was used in only 0.5% of procedures. No complication was observed during cardiac surgery.

The rate of anaesthetic complications was significantly higher in infants (4.3 per 1000) than in children (0.5 per 1000) ($P < 0.001$). Patients younger than 15 yr had a significantly lower risk than adults. The same was true when considering only the complications associated with cardiac arrest or the deaths (table III).

Complications, and the time of their occurrence, are shown for infants and children in tables IV and V, respectively.

In infants, complications occurred mainly during the maintenance of anaesthesia (table IV), whereas in children, many complications occurred at induction or during the postanaesthetic period (table V). The delay in occurrence of postanaesthetic complications was short in most of the patients, six out of eight being observed within the first 1 h following the conclusion of surgery.

Of the nine accidents observed in infants, seven were respiratory complications. In children, respiratory complications were seen as frequently as circulatory complications.

Airway mismanagement (five patients). This term meant a wrong choice of airway management technique, presumed to be responsible for the complication. Included in this group are: lack of tracheal intubation (one patient); premature extubation (one); bronchospasm in one patient having an history of allergy and whose trachea was intubated; asphyxia during inhalation anaesthesia in two patients with upper airway tract anomalies.

Complication of intubation (four patients). This group included technical incidents of tracheal intubation. These were: right lung selective intubation (one); unintentional extubation (one); obstruction of tube by secretions (one); aspiration in one patient during intubation of the trachea.

Aspiration (four patients). Included in this group are cases of aspiration occurring in patients in whom the trachea was not being intubated.

TABLE IV. *Causes of anaesthetic complications and the time of their occurrence in infants (< 1 yr)*

	Time of occurrence		
	Induction	Maintenance	Recovery
Respiratory complications			
Airway mismanagement	1	2	—
Complication of intubation	—	2	—
Inhalation of vomit	—	1	1
Circulatory complications			
Sudden cardiac arrest	—	1	—
Acute pulmonary oedema	—	—	1
Total	1	6	2

TABLE V. *Causes of anaesthetic complications and the time of their occurrence in children (1–14 yr).* † *One death*

	Time of occurrence		
	Induction	Maintenance	Recovery
Respiratory complications			
Airway mismanagement	—	1	1
Complication of intubation	1	1	—
Inhalation of vomit	1	—	1
Respiratory depression	—	—	2†
Failure of equipment	1	—	—
Circulatory complications			
Sudden cardiac arrest	1	—	—
Halothane overdose	1	1	—
Anaphylactoid shock	2	1	—
Acute pulmonary oedema	—	—	1
Severe arrhythmias	—	1	1
Total	7	5	6

Although this complication should have been classified in the "airway mismanagement" group, it has been individualized because it represents a major matter of concern in anaesthesia. Two of these episodes occurred during anaesthesia and the other two during the recovery period.

Postoperative respiratory depression. In two patients classified in this group, narcotic analgesics had been administered, for which antagonists had not been used. One of these episodes led to the death of a child of 13 yr.

Failure of equipment (one patient). This event followed a wrong mounting of the ventilator valve.

Halothane overdose. One occurred during induction and another during maintenance of anaesthesia, in patients breathing spontaneously.

Anaphylactoid shock. Althesin was incriminated in one patient, suxamethonium in another and, in the third, the circulatory failure followed a blood transfusion.

Acute pulmonary oedema. This complication, in two patients, was the result of fluid overload.

Severe arrhythmia. This occurred during maintenance, in a child undergoing circumcision, when inadequate analgesia was incriminated by the anaesthetist; and at recovery, in a patient operated on for peritonitis with septic shock. An electrolyte imbalance might have been responsible for this latter accident, judged to be partially related to anaesthesia.

Cardiac arrest (two patients). In both patients, no obvious cause was reported by the anaesthetist involved with the case. One of these events was followed by mild neurological sequelae and the other was associated with pericarditis followed by complete recovery.

With the exception of cardiac arrest, an example of each of these complications is illustrated in greater detail in table VI.

Risk factors

The anaesthetic risk was closely related to the patient's preoperative condition. It increased markedly with ASA score (rate of complications > 10 per 1000 for patients ASA $\geqslant$ III) and with co-existing diseases (rate of complications > 20 per 1000 with three or more co-existing diseases) (table VII). Concurrent airway infection was present in two patients with complications. Hypovolaemia was mentioned in one patient with complications and anaemia in another. Other co-existing diseases were mainly congenital anomalies. Patients who had previously been anaes-

TABLE VI. *Cases illustrative of complications. sux. = Suxamethonium*

Complication	Age/sex	Weight (kg)	Co-existing diseases	ASA status	Preoperative diagnosis	Anaesthesia	Time of occurrence	Comment	Outcome
Airway mismanagement	5 month/ M	6	Bronchitis	II	Inguinal hernia +ectopic testis	I.v.+halothane +N_2O No tracheal intubation	Maintenance	Laryngospasm Bradycardia Cardiac arrest	Recovered
Complication of intubation	1 day/M	4	No	IIIE	Anal atresia	Halothane+N_2O +tubocurarine narcotic analgesic	Maintenance	Right lung selective intubation	Recovered
Inhalation	7 yr/M	23	No	I	Appendicitis	I.v.+halothane +N_2O No tracheal intubation	Recovery	Laryngospasm+ bronchospasm (full stomach)	Recovered
Respiratory depression	13 yr/M	36	No	I	Fractured wrist (reintervention)	I.v.+N_2O+sux. +narcotic analgesic +neuroleptic	Recovery	Coma discovered in ward, 4 h after end of surgery	Died
Failure of equipment	8 yr/F	23	No	I	Congenital hip dysplasia	I.v.+halothane +N_2O+sux.+ narcotic analgesic	Induction	Wrong mounting of ventilator valve Cardiac arrest	Recovered
Sudden cardiac arrest	1 month/ F	5	Previous hypocalcaemia	II	Hip osteoarthritis	Halothane+N_2O	Maintenance	?	Mild neurological sequelae
Halothane overdose	1 yr/F	7	Multiple congenital anomalies	IV	Renal dysplasia	Sux.+3% halothane Spontaneous ventilation	Maintenance	Ventricular arrhythmias Circulatory arrest	Recovered
Anaphylactoid shock	14 yr/M	66	No	I	Hirschprung's disease	I.v+N_2O+sux.+ tubocurarine+neuroleptic +narcotic analgesic	Induction	Shock to Althesin	Recovered
Acute pulmonary oedema	10 yr/M	28	Hypovolaemia Hypothermia	IIE	Open fractured leg	I.v.+halothane+ N_2O+sux.+ narcotic analgesic	Recovery	Preoperative fluid overload Insufficient rewarming	Recovered
Arrhythmia	2 yr/M	12	Septic shock	IIIE	Peritonitis	I.v.+halothane +N_2O+tubocurarine	Recovery	Electrolyte imbalance?	Recovered

TABLE VII. *Incidence of anaesthetic complications (number, and rate per 1000) according to risk factors (infants and children grouped together). †Group ASA I* v. *groups ASA II, III, IV+V. §Groups with 0 or 1 co-existing disease* v. *groups with 2 or ≥ 3 co-existing diseases*

	No. anaesthetics	Major complications		P
		No.	Rate	
ASA class				
I	36 903	14	0.4	0.001†
II	1 461	5	3.4	
III	518	6	11.6	
IV+V	122	2	16.4	
No. co-existing diseases				
0	36 544	18	0.5	0.001§
1	3 064	4	1.3	
2	490	2	4.1	
≥ 3	142	3	21.1	
Previous anaesthetic				
No	27 517	14	0.5	0.05
Yes	11 343	13	1.1	
Duration of preoperative fasting (h)				
< 8	5 189	8	1.5	0.05
≥ 8	34 067	19	0.6	
Emergency				
No	33 391	18	0.5	0.05
Yes	5 918	9	1.5	

thetized were more prone to complications than those undergoing a first anaesthetic. Full stomach (defined as a preoperative fasting period of less than 8 h) was also associated with a higher complication rate. Complications appeared three times more frequently during emergency than during elective procedures (table VII).

DISCUSSION

We have previously commented on the design of this study [5], but certain points are worth re-emphasizing. There is a possible underestimation of non-lethal complications, since the accuracy of notification could be confirmed only for the deaths. The survey did not include complications occurring after the 24 h. Because of the absence of co-existing diseases in most of the paediatric patients, these delayed complications are even less frequent in children than in adults.

The mortality rate observed in this study was very low (1 in 40000). Smith [6] gave similar figures, provided by two paediatric institutions: no death in 37000 cases of tonsillectomy, one anaesthetic death in 29000 procedures of all types. The fact that anaesthetic mortality has decreased markedly in the paediatric population during the past 20 years [1,2] is sufficient reason for studies of this type to be extended to include morbidity. The rate of cardiac arrests in our study (0.3 per 1000) was lower than in the survey reported in 1961 by Rackow, Salanitre and Green [1] (0.7 per 1000), but it was not different from that reported by Salem and colleagues in 1975 [4]. In keeping with previous reports [1,7,8], the risk of complications was higher in infants than in children.

As a group, patients younger than 15 yr had a morbidity and mortality risk lower than adults—the opposite of the earlier results [1,2]. This reversal of trends probably reflects the improvements in paediatric anaesthesia during the past 20 years. However, the risk of anaesthetic cardiac arrests has been observed to be greater in patients younger than 12 yr than in adults, although most occurred in infants [9].

Comparison of accidents in infants with those in children revealed marked differences. Whereas complications observed in infants occurred mainly during the maintenance of anaesthesia and were the result of respiratory failure, circulatory failure was as frequent as respiratory failure in children. In addition, accidents were divided almost equally during the three periods of anaesthesia in the > 1 yr paediatric population. The fact that the only death occurred during the recovery period emphasizes again that this period is particularly critical [5].

This study highlighted the predominant role played by the patient's preoperative condition in the occurrence of complications. However, in retrospect, most of the complications seemed avoidable.

Although interpretation of the data reported here must take into account problems specific to clinical practice in France, this study represents the first prospective study of anaesthetic morbidity in the paediatric age group.

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MEASUREMENT OF EVOKED DIAPHRAGM TWITCH STRENGTH DURING ANAESTHESIA

Adaptation and Evaluation of an Existing Technique

M. C. DERRINGTON AND N. HINDOCHA

SUMMARY

The technique of recording the mechanical response of the diaphragm after the transcutaneous stimulation of the phrenic nerve, during anaesthesia and surgery, is described in patients undergoing non-abdominal surgery. The pressure difference generated across the diaphragm after phrenic nerve stimulation was derived from the simultaneous recording of gastric and oesophageal pressures with air-filled balloon catheter systems. This was recorded as the diaphragm "twitch" in a manner similar to that of peripheral muscles. Special problems encountered in the use and the validation of the technique in the anaesthetized patient are considered.

The respiratory muscles are particularly vulnerable during and after anaesthesia, but objective investigation of their function during this period has received little attention. In conscious subjects the strength and endurance of the diaphragm have been assessed [1–4] by the measurement of the pressure gradient across the muscle during voluntary ventilatory manoeuvres and loaded breathing; these tests cannot be applied easily after anaesthesia and surgery. The production of an involuntary contraction of the diaphragm by electrical stimulation of the phrenic nerve has been used to make an objective assessment of diaphragm strength [5], to investigate the development of diaphragmatic fatigue [6] and to examine the effects of drugs on both of these [7].

The first report of stimulation of the phrenic nerve, with observation of the response of the diaphragm, in an anaesthetized patient was probably that of Dripps [8], who investigated whether prolonged apnoea was peripheral or central in origin. The electromyographic (EMG) response of the diaphragm, after stimulation of the phrenic nerve, has been recorded during anaesthesia [9] and used to calculate dose–response curves for pancuronium in the diaphragm. Chauvin [10] recorded the diaphragm twitch strength and the effect of vecuronium using needle electrodes for bilateral phrenic nerve stimulation.

We describe a technique of recording the mechanical twitch response of the diaphragm after unilateral transcutaneous stimulation of the phrenic nerve, which is applicable during and after surgery. Special attention is given to the problems encountered in adapting the technique for use in the anaesthetized patient and to the validation of the measurements during anaesthesia.

METHODS

Principle

When the phrenic nerve is stimulated the diaphragm descends, rendering pleural pressure (Ppl) negative and abdominal pressure (Pab) positive. The pressure gradient developed across the diaphragm (transdiaphragmatic pressure, Pdi) is proportional to the contractile strength of the diaphragm and is obtained by subtracting intrapleural from intra-abdominal pressure:

$$P\text{di} = P\text{ab} - P\text{pl}$$

Pdi can be used as the "diaphragm twitch" in a manner similar to that in which adductor pollicis twitch has been recorded with a strain gauge to assess muscle strength peripherally [11, 12]. As

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with any muscle, the magnitude of diaphragmatic contraction is dependent on its length before stimulation [13]; therefore, it is very important that the height of *P*di is measured at a standard lung volume. An abdominal strain gauge monitors chest wall configuration and twitches are compared after stimulation at resting end-expiration (FRC). Pleural and abdominal pressures are measured using air-filled oesophageal and gastric balloons, respectively.

The pressure within the oesophageal balloon will approximate to pleural pressure only if the pressure difference across all intervening structures is zero. These conditions are achieved if the oesophageal balloon volume is 0.2 ml or less [14]. Milic-Emili [15] reported that placement of the oesophageal balloon in the middle one-third of the oesophagus was associated with most reliable measurements approximating to pleural pressure. This requires a catheter length of about 30–40 cm from the lips.

Patients and procedure

Approval for the study was obtained from the District Ethics Committee. We studied fit patients undergoing non-abdominal surgery. Full informed consent was obtained and premedication was given, according to the usual practice of the anaesthetist, using either a benzodiazepine or an opioid and antisialagogue or antiemetic.

Anaesthesia was induced with thiopentone and the trachea intubated after the administration of suxamethonium. The patients breathed halothane and 60% nitrous oxide in oxygen; opiates were given i.v. as appropriate. As soon as the patient was asleep, an abdominal strain gauge was placed around the waist 2 cm above the umbilicus to monitor chest wall configuration. Latex rubber balloons, 10 cm in length (P. K. Morgan Ltd) were placed in the oesophagus to record pleural pressure and in the stomach to record intra-abdominal pressure. These were attached via air-filled catheters to identical pressure transducers (Elcomatic EM 751A). Balloon placement was achieved by passing a soft-ended wire down the lumen of each balloon catheter and then introducing both catheters into an orogastric tube, the end of which had been cut off and softened. The tube was advanced into the stomach from the mouth and removed, leaving the balloons *in situ*. After extraction of the wires, the balloons were placed in the optimum position by attachment to the pressure transducers and slow withdrawal with close attention to the pressure traces. The oesophageal balloon was positioned where least interference by cardiac artefact was visible, and the catheters were secured by tape to the side of the cheek. The oesophageal and gastric balloons were inflated with 0.2 and 0.5–1.5 ml of air, respectively.

All three records (output of the abdominal strain gauge, gastric pressure (*P*ga) and oesophageal pressure (*P*oe)) were displayed on three channels of a six-channel chart recorder (Gould 2600 s) and *P*di—obtained by electronic subtraction (*P*ga − *P*oe)—was displayed simultaneously on a fourth channel (fig. 1). The pressure channels were calibrated with a water manometer before and after each investigation.

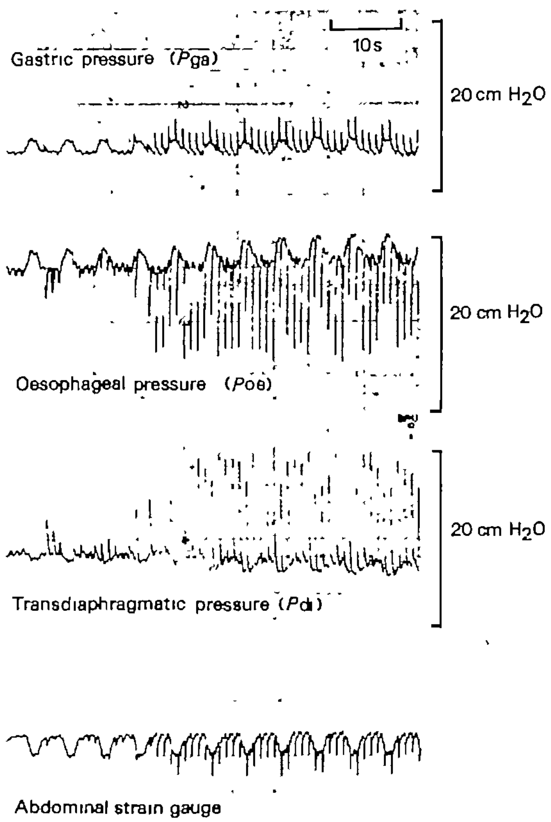

FIG. 1. Changes in gastric and oesophageal pressure in a mechanically ventilated patient during searching for the phrenic nerve and during phrenic nerve stimulation at a rate of 1 Hz. Transdiaphragmatic pressure is obtained by electronic subtraction of oesophageal from gastric pressure. Full scale deflection in each pressure trace is 20 cm H_2O and paper speed is 2 mm s^{-1}. The bottom trace shows abdominal strain gauge output

The phrenic nerve was stimulated transcutaneously behind the lateral head of the sternomastoid muscle. A hand-held pencil electrode was used with a saline-soaked felt tip, the indifferent electrode being placed on the sternum. The current, adjustable to a maximum of 35 mA into a 5-kΩ load, was generated by a programmable nerve stimulator (Bard Bio-Medical Peripheral Nerve Stimulator 750 digital) and had a stimulus width of 200 μs. Left and right phrenic nerve stimulation was attempted and the side associated with the better signal was continued for the purposes of the study. Supramaximal stimulation was ensured by increasing stimulator output 10–20% above that producing the greatest response from the diaphragm.

Validation of the technique during anaesthesia was then attempted as follows:

(1) The absolute values of *P*di obtainable in the anaesthetized patient were measured.

(2) System variability was tested by examination of the *P*di trace obtained after supramaximal phrenic nerve stimulation at 1 Hz during 10 consecutive breaths.

(3) The optimum stimulation frequency for the production of a clearly discernible and interpretable record of onset and recovery of neuromuscular blockade on the diaphragm was investigated.

(4) The accuracy with which recovery of diaphragm function could be monitored was assessed. This entailed searching constantly for the phrenic nerve in the area of stimulation, and measuring the height of the first discernible diaphragmatic twitch.

RESULTS

Table I lists the values of transdiaphragmatic pressure generated during anaesthesia after supramaximal phrenic nerve stimulation in nine patients after right-sided stimulation (mean 11.7 cm H_2O, range 7.9–15.8) and in four patients after left-sided stimulation (mean 14.3 cm H_2O, range 11.8–17.5).

The coefficient of variation of *P*di in 13 patients with stimulation at end-expiration over 10 breaths each was a mean of 3.7% (range 2–5.3%).

TABLE I. *Transdiaphragmatic pressures (*P*di) in the anaesthetized patient after unilateral supramaximal stimulation. Age, sex, side of stimulation and coefficient of variation over 10 breaths. Overall coefficient of variation = 3.7%*

Age (yr)	Sex	Side	*P*di (cm H_2O)	Coeff. variation (%)
23	Male	Right	15.8	4.6
36	Male	Right	10.2	2.0
66	Female	Right	7.9	2.6
64	Male	Right	11.0	3.1
30	Female	Right	13.3	3.4
52	Male	Right	13.6	4.8
60	Male	Right	12.6	5.3
50	Female	Right	10.2	3.8
37	Female	Right	10.4	4.0
Mean			11.7	3.7
46	Female	Left	13.2	4.7
61	Male	Left	17.5	2.3
31	Female	Left	14.6	3.0
63	Male	Left	11.8	3.8
Mean			14.3	3.4

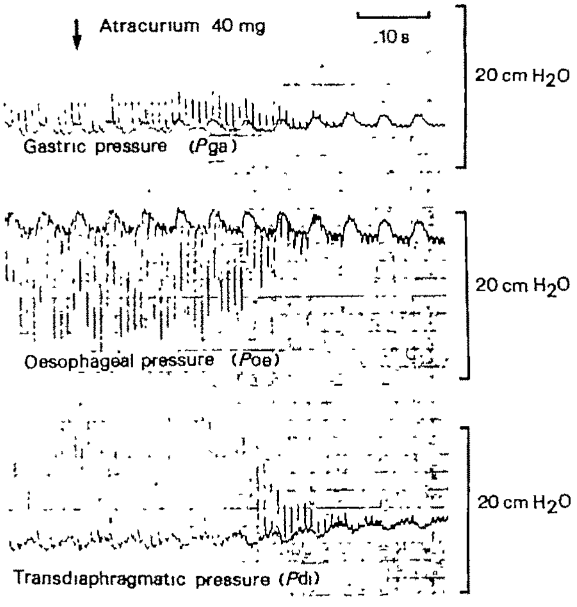

FIG. 2. Recording of gastric, oesophageal and transdiaphragmatic pressures with supramaximal phrenic nerve stimulation at a frequency of 1 Hz during the onset of neuromuscular blockade in the diaphragm after administration of atracurium.

In preliminary studies with neuromuscular blocking drugs it was found that, although the onset of neuromuscular blockade in the diaphragm was seen most clearly with stimulation at a frequency of 1 Hz (fig. 2), recovery of diaphragmatic function was most easily monitored using train-of-four stimuli at a frequency of 2 Hz every 10 s. This pattern of stimulation produced twitches which were clearly seen against the background noise caused mainly by cardiac

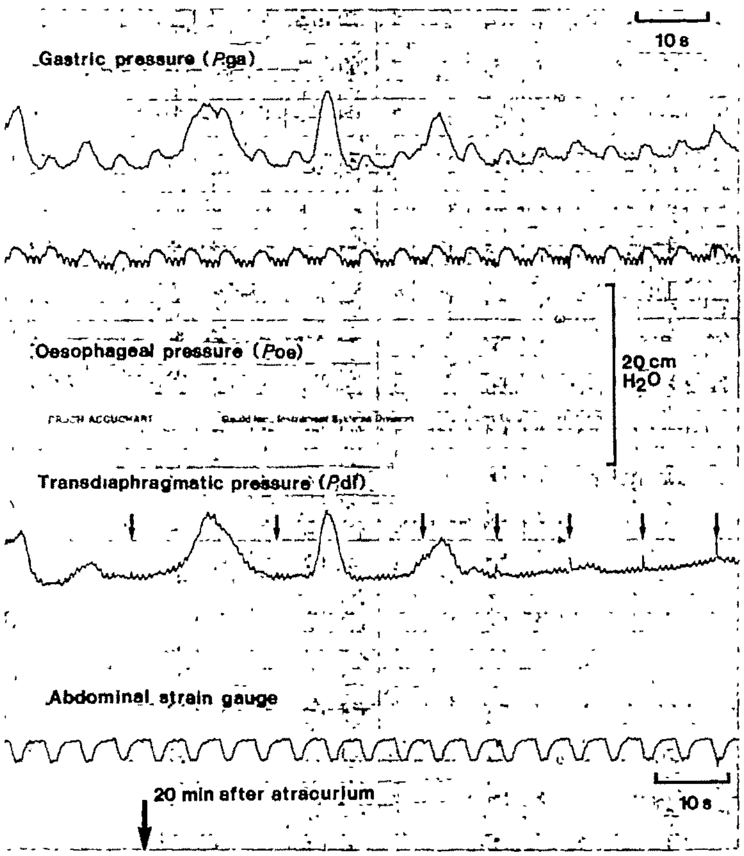

FIG. 3. Recording of gastric, oesophageal and transdiaphragmatic pressures and abdominal strain gauge output during initial recovery from neuromuscular blockade in the same patient as in figures 2 and 4. The phrenic nerve is stimulated with a train-of-four at a frequency of 2 Hz every 10 s. Paper speed 2 mm s^{-1} Full scale deflection in the pressure traces 20 cm H_2O.

pulsation, which is often at a frequency close to 1 Hz (figs 3, 4) and could be compared with established techniques of monitoring neuromuscular transmission such as the Myograph [16]. Figure 5 shows the recovery of neuromuscular function with time in the adductor pollicis muscle of the same patient, following the administration of atracurium. The traces are similar except for the absence of background noise in the Myograph.

In practice, recovery of function in the diaphragm was always found with just one twitch of the train-of-four present, and this was always very small. The amplitudes of the first discernible signal, in each of 10 patients, on recovery of diaphragm function after neuromuscular blockade are listed in table II.

DISCUSSION

We set out to evaluate the recording of evoked diaphragm twitch during anaesthesia and surgery and to develop a safe technique which could be used to monitor the onset and recovery of neuromuscular blockade in the diaphragm with minimum interference to anaesthesia and surgery.

Transcutaneous phrenic nerve stimulation was used in a manner similar to that described by Sarnoff [17]. To summarize his suggestions: the operator should be at the head of the table upon which the patient lies. The patient's head should be in the midline, slightly elevated from the table by a pillow, so both head and neck are slightly flexed—this relaxes the sternomastoid muscle so that it can be moved medially. The phrenic nerve

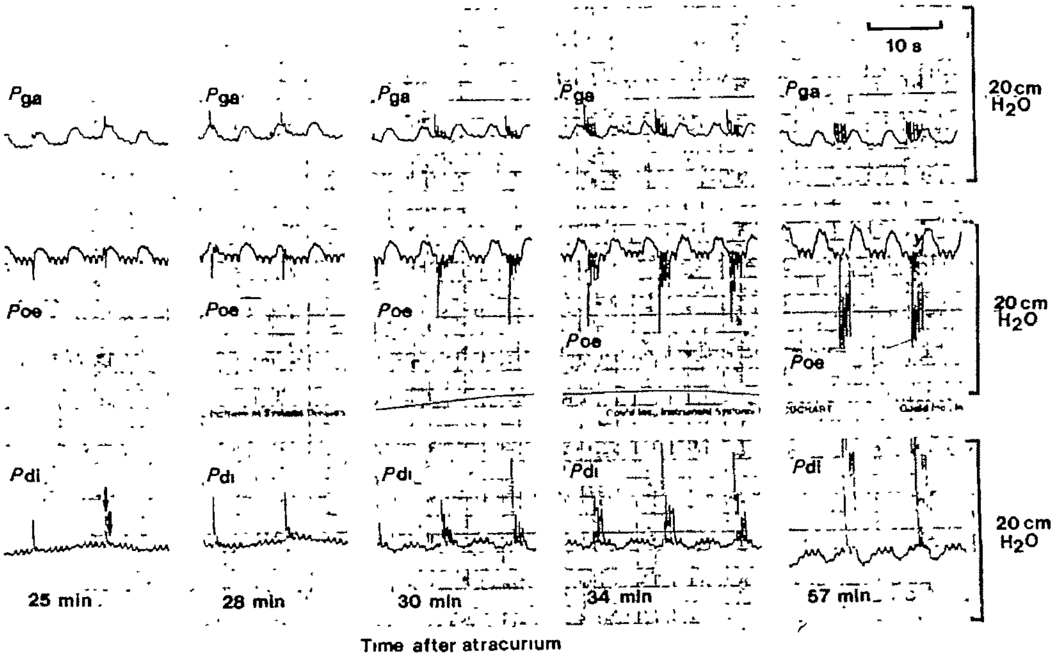

FIG. 4. Recording of gastric pressure (*P*ga) (top row), oesophageal pressure (*P*oe) (middle) and transdiaphragmatic pressure (*P*di) (bottom row) after administration of atracurium in the same patient as in the previous figures. Supramaximal phrenic nerve stimulation was by train-of-four at a frequency of 2 Hz every 10 s. Full scale deflection in each trace is 20 cm H_2O and paper speed 2 mm s^{-1}.

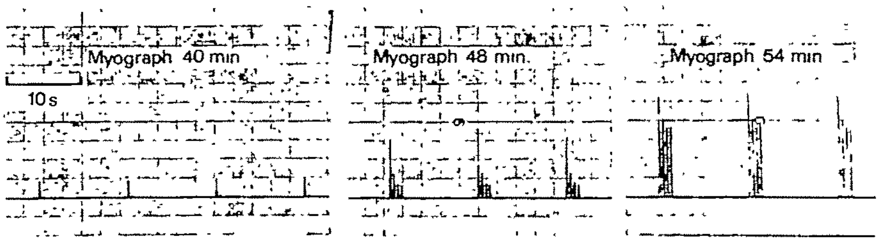

FIG. 5. Recording of the Myograph output in the same patient as in previous illustrations, showing the recovery of adductor pollicis twitch with time after administration of atracurium, demonstrating the relative absence of background noise.

is stimulated where it lies beneath the sternomastoid muscle, which must be displaced medially so current just passes through skin and platysma. The clavicular head of the muscle is often overlooked because it is a flat band, so it is important to search for it specifically. The stimulating electrode should be turned to face posteriorly to permit better contact with the surface of the anterior scalene muscle. Exploration for the nerve should begin one-third of the way

TABLE II. *Size of the first discernible transdiaphragmatic pressure (Pdi) twitch on spontaneous recovery of neuromuscular transmission in the diaphragm following administration of neuromuscular blocking drugs in the anaesthetized patient*

Patient		*Pdi* twitch	
Sex	Age (yr)	Actual size (cm H_2O)	(% control)
Male	23	0.4	2.5
Male	36	0.8	8.0
Female	66	0.6	7.6
Male	64	0.4	3.6
Female	30	0.6	4.5
Male	52	1.2	8.8
Male	60	0.8	6.4
Female	50	0.6	6.0
Female	46	1.0	7.6
Female	37	0.8	7.7
Mean		0.6	6.3

TABLE III. *Values of transdiaphragmatic pressure (Pdi) obtained on unilateral supramaximal phrenic nerve stimulation. Comparison between workers*

			Pdi (cm H_2O)	
Source	Subjects	Side	Mean	Range or SD
This study	Anaesthetized patients	Right	11.6	7.9–15.8
		Left	14.3	11.8–17.5
[20]	Awake volunteers	Right	10.3	±1.7
		Left	12.7	±2.2
[18]	20 normal males	Right	8.4	(no range quoted)
		Left	12.4	

between clavicle and mastoid, up and down the lateral ridge of the anterior scalene muscle. If cervical or brachial plexus motor activity occurs initially, stimulation should be attempted more medially.

Bilateral phrenic stimulation with needle electrodes has been described during anaesthesia [10], but we believe that this is potentially hazardous because of the proximity of structures such as major blood vessels, the lung and the vagus nerve, and because of the risks inherent in the breaching of the electrical resistance of the skin.

We used unilateral phrenic nerve stimulation in the operating theatre because it was felt that bilateral stimulation was too obtrusive for the anaesthetist to monitor the patient to his satisfaction, and because it was easier to maintain reliably for long periods the position of the stimulating electrode on the nerve. Right phrenic nerve stimulation is generally easier for the right-handed operator. However, in some patients following right-sided stimulation, the change in gastric pressure is biphasic, absent or even negative in direction. Stimulation of the left phrenic nerve in these patients produces an increase in gastric pressure. In one patient, a similar discrepancy was observed except that stimulation of the left phrenic nerve produced the smaller change in gastric pressure. This phenomenon has been described previously [18].

We were able to achieve supramaximal stimulation of the phrenic nerve transcutaneously and obtained *P*di values equivalent in magnitude to those reported in awake subjects [18, 19] (table III). The current output of the stimulator used is a function of the skin resistance of the individual subject (adjustable to 35 mA into a 5-kΩ load) and was usually about 20% more than that required for maximal stimulation. If too large a stimulation current was used, there was unintentional brachial plexus stimulation or direct stimulation of the muscles in the neck, causing the head to jerk to one side. In one or two patients, with very short, fat necks, supramaximal stimulation could not be achieved and further study was not possible. Once accustomed to the technique of phrenic stimulation it was easy for the operator to find the nerve and to keep the electrode in place for long periods in the majority of subjects. This has been the experience of other investigators—location and stimulation of the phrenic nerve in 75 patients, 24 of whom had severe diaphragm weakness, took on average 2.8 min [20] and, in 24 consecutive normal volunteers [17], 2–4 s "explore time" was necessary to find the nerve. Electrical interference with the electrocardiograph (ECG) occurred if the ECG electrodes were too close to the indifferent electrode on the sternum. Patients with pacemakers were excluded from our study because of the possibility of electrical interference with pacemaker sensing and output.

Gastric and oesophageal pressures were recorded by means of an air-filled balloon catheter system attached to identical pressure transducers, as used extensively by respiratory physiologists for many years. There are substantial differences in balloon placement between the anaesthetized and the awake subject. In the awake subject, the balloons are swallowed with relative ease after passage through the nares, and their position is then confirmed by means of voluntary ventilatory manoeuvres such as vital capacity breaths or maximal sniffs. Balloon placement was carried out in the present study after the induction of anaesthesia, to minimize delay and to facilitate patient recruitment to the study. In addition, the possibility of slightly increased risk of regurgitation during induction of anaesthesia with the balloons *in situ* could not be excluded. The pliable nature of the balloons renders direct insertion without coiling or kinking virtually impossible. It was necessary, therefore, to develop a reliable method of insertion in the anaesthetized patient. The measurement of absolute pleural pressure in the supine posture is contentious, since the weight of the mediastinal contents exerts a hydrostatic force of its own which varies along the length of the oesophagus. Drummond [21] has questioned the validity of the measurement of oesophageal pressure to estimate pleural pressure in the supine anaesthetized patient, but other workers [22–24] have shown values of oesophageal pressure: mouth pressure ratio within 10% of unity. Provided that the balloon is firmly fixed during stimulation, it is certainly valid to observe relative changes in transdiaphragmatic pressure within one patient.

Chauvin [10], using a similar technique, reported the effect of vecuronium on the diaphragm in patients anaesthetized with 60% nitrous oxide in oxygen and given bolus doses of fentanyl and thiopentone. In his study, tracheal intubation was carried out under local anaesthesia. We used suxamethonium to facilitate tracheal intubation and the passage of the balloons. Halothane was administered to provide smooth anaesthesia and to minimize the risk of awareness. Halothane has the least effect on neuromuscular transmission of the inhalation agents in common use [25, 26], although our results may have been influenced by its administration and by any residual effects of the suxamethonium.

Limitations of the method include the fact that it is only applicable during operation in patients undergoing anaesthesia for non-abdominal surgery. The principle of the technique relies upon an intact abdominal cavity, but diaphragmatic recovery could be tested after the abdomen was closed, when indicated. Isometric contraction of the diaphragm cannot be studied by this technique. Aubier [16] described the application of casts to the torso of his subjects so as to prevent distortion of the abdominal wall. It may be argued, however, that it is of much greater clinical relevance to study the effective diaphragm strength, rather than such a contrived situation. When transdiaphragmatic pressure is measured after the administration of neuromuscular blocking drugs, the muscles of the abdominal wall are paralysed so that return of function in the diaphragm is measured with what may be a flaccid abdominal wall, preventing efficient diaphragmatic function. The effect resulting from the paralysis of the abdominal musculature would be more apparent in the gastric pressure trace, so it is important to measure the changes in both oesophageal and gastric pressures. As the relative contribution to *P*di of gastric or oesophageal pressure varies between individuals, the measurement of pressure on both sides of the diaphragm is advisable.

There is a potential source of error when searching for return of function in the diaphragm. It is possible that the actual return of function precedes the demonstration of the first twitch by an unknown and unmeasurable amount. This must be taken into account when comparisons between return of function in peripheral musculature and diaphragm are made. It must be pointed out that the error is in a direction which emphasizes patient safety, in that return of function in the diaphragm would be detected at a later stage. The twitches resulting from diaphragm contraction may not be discernible when they are very small, because of extraneous noise on the trace. Cardiac artefacts may be prominent, especially on the oesophageal trace. This difficulty may be overcome by measuring the time taken for return or disappearance of twitch when it is 10% or 20% of control.

Established methods of assessing diaphragm function after anaesthesia are far from ideal. Apart from clinical appearance and simple measurements of respired volume and gas exchange, it is very difficult to measure the function of the respiratory muscles in unco-operative, partially anaesthetized patients. Although the maintenance of ventilation has been considered an acceptable test of respiratory muscle function, it is insensitive to considerable losses of respiratory muscle strength which may go unobserved and result in delayed ventilatory failure or the inability to cough. It is, therefore, important to develop a safe method for assessing the recovery of ventilatory function of the muscles of ventilation following the administration of myoneural blocking drugs in a manner similar to that which is available for the peripheral muscles [27]. The techniques which have been described include the study of partially curarized awake volunteers [28–34], the administration of low doses of neuromuscular blocking drugs to patients breathing spontaneously with measurement of end-tidal carbon dioxide concentration [35] and the assessment of such ventilatory variables as tidal volume, minute ventilation and airway occlusion pressure in patients following operation [36, 37]. These tests, generally, rely on voluntary co-operation or assume intact unimpaired central control of ventilation.

The diaphragm is unique among the muscles of ventilation in that its strength can be recorded independently by measuring the pressure gradient developed across it after stimulation of one or both phrenic nerves [38].

The EMG response of the diaphragm after stimulation of the phrenic nerve has been recorded during anaesthesia [9], but this may be unsatisfactory as a quantitative assessment of diaphragm function, for two reasons. First, the EMG signal from surface and oesophageal electrodes, which are not in permanent contact with the diaphragm, will vary according to the distance between recording electrodes and the muscle at different phases of its contraction [39]. An alternative approach might be to use needle or wire electrodes in the diaphragm, but the resulting signals would still not reflect the action of the muscle as a whole. Furthermore the technique has greater attendant risks, especially in the operating theatre. Second, an increasing magnitude of electromyographic response has been demonstrated alongside a diminishing force of contraction in dogs using a model of diaphragmatic fatigue [40]. It is difficult to predict whether there are other situations in which the magnitude of the force of contraction and the EMG signal do not move in parallel, so it would seem better to measure the force of contraction directly.

Recently, Dodgson [41], using infusions of tubocurarine in awake subjects, has suggested that paralysis of the musculature in the upper airway impairs breathing by increasing inspiratory resistance. It is difficult to extrapolate the results of work carried out on conscious volunteers to the clinical situation, especially when subclinical doses of neuromuscular blocking drugs are used, but it may be that this, rather than residual diaphragm weakness, is of major importance in the development of ventilatory problems in the postoperative period. In addition, it could be argued that a combination of the two factors may operate in the postoperative period: residual diaphragm paralysis impairing cough and predisposing to chest infection and atelectasis, and weakness of the upper airway musculature causing obstruction and apnoea.

We have described the adaptation of a technique for measuring evoked diaphragm twitch for use during, and immediately following, anaesthesia and surgery. We recommend it as safe and easily applicable with minimum interference in the operating theatre schedule, but it is applicable only during operation in patients undergoing non-abdominal surgery. At present, it is probably best regarded as a research tool to compare and contrast the effects of neuromuscular blocking drugs on the different muscle groups, rather than as a routine clinical test. It may also have a clinical application in the assessment of patients with weakness of the muscles of ventilation after anaesthesia and surgery.

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COMPARISON OF NEUROMUSCULAR BLOCKADE IN THE DIAPHRAGM AND THE HAND

M. C. DERRINGTON AND N. HINDOCHA

SUMMARY

Neuromuscular blockade was recorded in the diaphragm and in the adductor pollicis muscle using unilateral supramaximal stimulation of phrenic and ulnar nerves and measurement of the mechanical effect of each. After administration of atracurium 0.4–0.5 mg kg^{-1} to 10 patients, both onset and recovery of neuromuscular blockade in the diaphragm occurred before that in adductor pollicis and there was a linear relationship between recovery in diaphragm and adductor pollicis. After administration of vecuronium 0.08–0.1 mg kg^{-1} to a further 10 patients, paralysis occurred in the diaphragm before adductor pollicis in all except one patient, in whom it occurred simultaneously. Reappearance of adductor pollicis twitch occurred in six patients after all four twitches had returned in the diaphragm, but the rate of recovery of twitch height in the diaphragm was more rapid than in adductor pollicis in every patient.

During anaesthesia, the common objective tests of neuromuscular blockade are confined to observation of function in peripheral skeletal muscles [1] and it is generally assumed that they provide valid information on respiratory muscle function. The justification for this has been derived from several studies which have attempted to relate peripheral and respiratory muscle function [2–7]. There is some evidence that the muscles of ventilation may be affected before the peripheral muscles following administration of neuromuscular blocking drugs. Norman and colleagues [8] found that patients given subclinical doses of neuromuscular blockers, during a steady state of anaesthesia, showed a decrease in peak expiratory flow and an increase in end-tidal carbon dioxide concentration before an effect was demonstrable on adductor pollicis twitch.

We have compared the onset and recovery of neuromuscular blockade in a peripheral and a respiratory muscle by recording the evoked mechanical response of adductor pollicis and of the diaphragm after administration of atracurium to 10 patients and of vecuronium to a further 10 patients.

PATIENTS AND METHODS

We studied patients undergoing varicose vein surgery. The study was approved by the local Ethics Committee and full informed consent was obtained from all patients. The anaesthetic technique was standardized: induction of anaesthesia with thiopentone and intubation of the trachea after administration of suxamethonium 1–1.5 mg kg^{-1}, spontaneous ventilation with halothane and 66% nitrous oxide in oxygen and opioids given as required. The drugs used for premedication and analgesia are listed in table I.

Evoked twitch in the diaphragm was recorded using the method described in the accompanying paper [9]. Oesophageal and gastric balloons were inserted and connected to pressure transducers (Elcomatic 751A), an abdominal strain gauge was placed around the waist, 2 cm above the umbilicus, to record abdominal girth as a monitor of chest wall configuration, and the phrenic nerve was stimulated in the neck behind the lateral head of the sternomastoid muscle (fig. 1). The Myograph [10] was used to record the twitch tension of the adductor pollicis evoked by stimulation of the ulnar nerve. Adductor pollicis twitch, gastric pressure, oesophageal pressure, transdiaphragmatic pressure (*P*di) and abdominal strain gauge output were displayed on a six-channel chart recorder.

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TABLE I. *Patients studied, details of premedication, neuromuscular blocker (NMB) and intraoperative opioid administered, control diaphragm twitch tension (Pdi), and side of stimulation. D = diazepam; T = temazepam; P+H = papaveretum and hyoscine; F = fentanyl; M = morphine; P = papaveretum*

Patient	Age (yr)	Sex	Weight (kg)	Pre-med.	Opioid	NMB	Control *Pdi* (cm H_2O)	Side
1	23	M	81	P+H	P	Atracurium 40 mg	15.8	R
2	36	M	75	D	P	Atracurium 35 mg	10.2	R
3	66	F	62	T	P	Atracurium 25 mg	8.0	R
4	64	M	110	T	M	Atracurium 50 mg	11.0	R
5	30	F	60	T	F	Atracurium 30 mg	13.3	R
6	52	M	78	D	P	Atracurium 35 mg	13.7	R
7	60	M	80	D	P	Atracurium 40 mg	12.6	R
8	55	F	70	D	F	Atracurium 30 mg	15.0	L
9	37	F	70	D	P	Atracurium 30 mg	10.4	R
10	44	F	68	T	M	Atracurium 30 mg	14.0	L
11	31	F	64	T	P	Vecuronium 6 mg	14.6	R
12	63	M	80	D	P	Vecuronium 6 mg	11.8	R
13	51	F	58	D	M	Vecuronium 5 mg	12.0	R
14	55	M	62	T	P	Vecuronium 6 mg	10.0	L
15	48	M	85	T	F	Vecuronium 7 mg	11.2	R
16	56	M	74	P+H	P	Vecuronium 6 mg	14.8	L
17	57	M	69	D	M	Vecuronium 6 mg	12.8	L
18	57	M	84	T	P	Vecuronium 7 mg	10.0	L
19	57	F	64	D	P	Vecuronium 5 mg	9.8	L
20	31	F	72	T	P	Vecuronium 7 mg	14.0	L

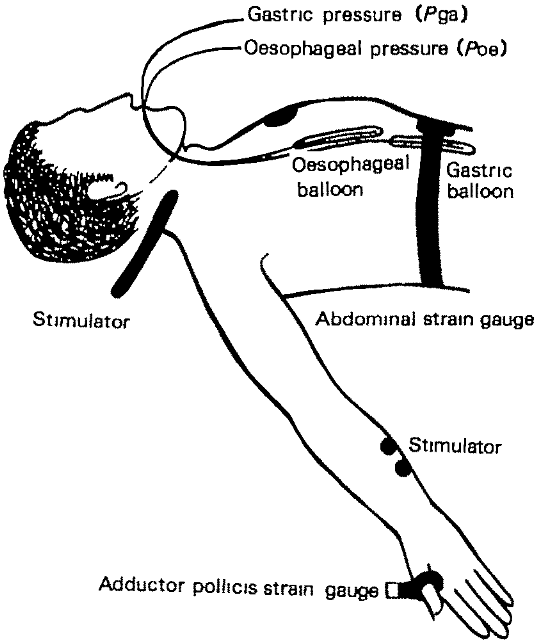


FIG. 1. Diagram of apparatus for comparison of evoked twitch in the diaphragm and in adductor pollicis. The Myograph is placed on the forearm to evoke and record twitch in adductor pollicis. Oesophageal and gastric balloons record the pressure difference across the diaphragm after stimulation of the phrenic nerve in the neck.

Supramaximal stimulation was commenced at a frequency of 1 Hz, and measurements were obtained over a few breaths so that control *P*di height could be measured at resting end expiration. The neuromuscular blocking drug was administered (fig. 2) and the onset of neuromuscular blockade was taken as the point of disappearance of twitch. Ventilation of the lungs was continued using a Manley ventilator with a fresh gas flow of 100 ml kg^{-1} min^{-1} and the concentration of halothane was reduced in the inspired gas mixture. Spontaneous recovery of each muscle was then sought and recorded using train-of-four (TOF) stimulation at a frequency of 2 Hz every 10 s (fig. 3). The time of spontaneous reappearance of the first twitch (T1) of the train-of-four was recorded in all patients for both the diaphragm ($T1_D$) and adductor pollicis ($T1_{AP}$) muscles. The time to recovery of the fourth twitch (T4) of the train-of-four also was recorded in the diaphragm in every patient, and in adductor pollicis when operating time allowed. The time at which $T1_D$ reached 50% of its control height (D_{50}), was recorded also. All measurements were obtained before antagonism of neuromuscular blockade and anaesthesia was not prolonged unnecessarily. If surgery was completed before

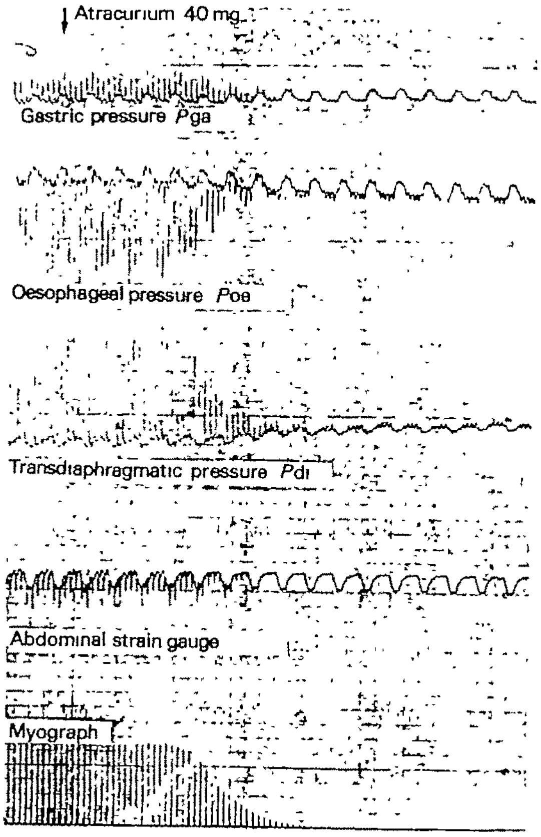


FIG. 2. Onset of neuromuscular blockade in the diaphragm and in the hand after administration of atracurium 40 mg with supramaximal stimulation at a frequency of 1 Hz. In the top three traces are gastric pressure (*P*ga), oesophageal pressure (*P*oe) and the electronic subtraction of these, the transdiaphragmatic pressure (*P*di). Full scale deflection in each of these traces is 20 cm H_2O. The fourth trace shows abdominal strain gauge output which records diaphragmatic configuration. The bottom trace shows the Myograph output

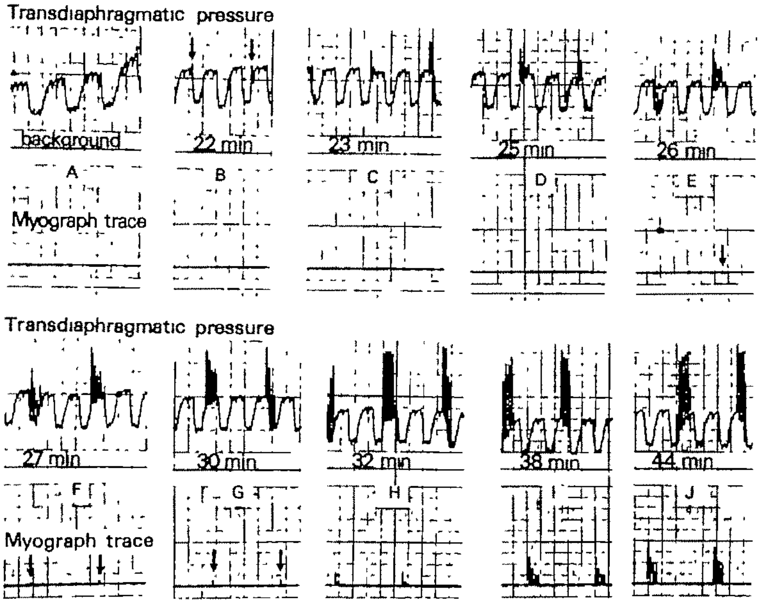
spontaneous recovery of neuromuscular transmission, the study was abandoned.

Ten patients (group 1) received atracurium 0.4–0.5 mg kg^{-1} and a further 10 patients (group 2), studied consecutively, received vecuronium 0.08–0.1 mg kg^{-1}.

RESULTS

Table I lists the demographic data for all the patients in the study, with the dose of blocking drug administered, the control transdiaphrag-

FIG. 3. Spontaneous reappearance of twitch with time after administration of vecuronium 0.1 mg kg^{-1} in diaphragm and adductor pollicis muscles with supramaximal train-of-four (TOF) stimulation of phrenic and ulnar nerves at a frequency of 2 Hz every 10 s. Transdiaphragmatic pressure is shown in the top trace, full scale deflection being 20 cm H_2O, with Myograph trace below. Each two small squares horizontally represents 1 s. A: Background traces with no diaphragm or adductor pollicis twitch. B: Single diaphragm twitch in response to TOF a few minutes after its reappearance. Panels C–J enable comparison of the degree of return of mechanical twitch in the two muscles with time.



matic pressure twitch tension and the side of phrenic nerve stimulation.

In all the patients given atracurium, the onset of paralysis in adductor pollicis was preceded by that in the diaphragm. Spontaneous return of all twitches of the train-of-four occurred in the diaphragm before there was any evidence of return of function in adductor pollicis (table II). After vecuronium, onset of paralysis in adductor pollicis was preceded by that in the diaphragm except in one patient (P11) in whom it occurred at the same time in both muscles. The pattern of recovery was more variable in this group. In one patient (P12) the reappearance of T1 in the diaphragm and in the hand was virtually simultaneous. In a further three patients $T1_{AP}$ appeared before all four twitches of the diaphragm TOF were visible. However, in the remaining six patients, all four twitches of the diaphragm had returned before there was any evidence of recovery in adductor pollicis (table II).

After administration of atracurium (fig. 4A), there was a close correlation ($r = 0.949$, $P < 0.001$ for T1; $r = 0.988$, $P < 0.001$ for T4) between the time of return of neuromuscular transmission in the diaphragm and that in adductor pollicis. No correlation was seen with vecuronium (fig. 4B).

The mean delay between return of neuromuscular transmission in the two muscles was 12.1 min after atracurium (95% confidence intervals 5.3–18.9 min) and 7.6 min after vecuronium (95% confidence limits −3.82 to 19.1 min) [11]. Although the duration of action of vecuronium on the diaphragm was more predictable (95% confidence intervals for complete

TABLE II. *Time of onset and recovery of neuromuscular blockade (NMB) after atracurium 0.4–0.5 mg kg^{-1} and vecuronium 0.08–0.1 mg kg^{-1} in the diaphragm (D) and in adductor pollicis (AP). For onset of blockade, time of disappearance of twitch with stimulation at a frequency of 1 Hz is recorded. The times of reappearance of first (T1) and fourth (T4) twitches of the train-of-four and the time when T1 of the diaphragm reached 50% of control (D_{50}) are also listed*

	Onset NMB (s)		Recovery NMB (min)				
Patient	D	AP	$T1_D$	$T4_D$	D_{50}	$T1_{AP}$	$T4_{AP}$
Atracurium group							
1	37	89	21.7	27.7	31.3	33.0	42.5
2	33	53	14.7	19.9	18.5	33.0	—
3	52	66	27.0	34.5	32.4	39.7	48.4
4	31	66	33.9	36.8	42.1	43.7	52.5
5	31	38	25.2	31.2	33.5	35.9	—
6	58	85	24.7	28.4	31.1	37.1	47.1
7	75	115	38.3	44.7	47.3	58.5	68.3
8	48	65	15.3	23.6	25.3	28.9	37.6
9	40	58	29.8	31.5	32.0	39.4	—
10	45	65	19.6	29.2	29.2	32.8	44.1
Mean	45	70	25.0	30.7	32.3	38.2	48.6
SD	13.9	21.5	7.6	6.9	8.0	8.3	9.9
Vecuronium group							
11	31	31	21.7	27.7	33.6	24.2	35.8
12	39	77	26.6	33.3	30.8	26.4	38.4
13	38	55	22.7	30.7	26.4	36.8	—
14	47	92	17.5	22.0	22.2	33.0	42.9
15	89	106	18.1	24.5	28.0	30.0	46.9
16	43	88	20.4	25.4	26.0	27.4	39.1
17	105	136	21.5	23.4	27.3	33.2	41.6
18	57	85	22.0	29.3	30.2	31.8	44.2
19	67	110	20.6	24.5	31.9	22.9	36.9
20	26	85	26.8	31.7	32.2	29.0	36.5
Mean	54.2	86.5	21.8	27.3	28.9	29.5	40.3
SD	25.8	29	3.1	3.9	3.5	4.3	3.8

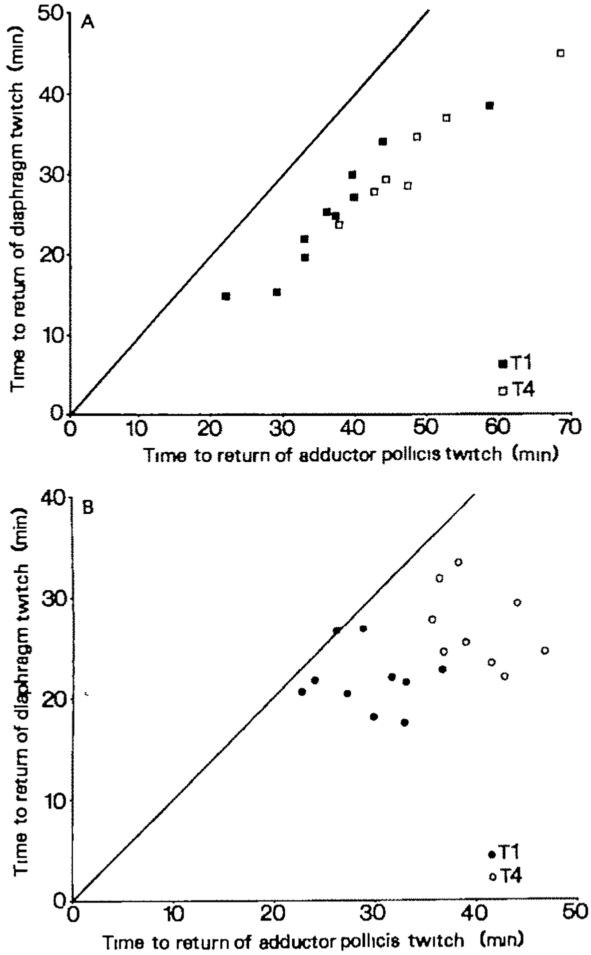


FIG. 4. Relationships between time to spontaneous reappearance of adductor pollicis twitch and diaphragm twitch after administration of atracurium 0.4–0.5 mg kg^{-1} (A) and vecuronium 0.08–0.1 mg kg^{-1} (B). Solid symbols denote time to reappearance of the first twitch of the train-of-four (TOF) and open symbols time to fourth twitch of the TOF. The line of identity is also displayed.

paralysis of the diaphragm being 15.6–28 min for vecuronium and 9.8–40.2 min for atracurium), the return of diaphragm twitch did not always precede that of adductor pollicis.

As an index of return of strength, the time of 50 % recovery of $T1_D$ was assessed for each drug (table II) and plotted against time of reappearance of $T1_{AP}$ (fig. 5); the relationship was linear ($r = 0.95$, $P < 0.001$) after atracurium administration. The mean delay between 50 % recovery of $T1_D$ and reappearance of $T1_{AP}$ was 4.8 min (95 % confidence intervals −1.36 to +11 min) for atracurium and 0.6 min (95 % confidence intervals −13.8 to +15.0 min) for vecuronium. Considering $T4_{AP}$ in a similar manner, mean difference was 14.5 min (95 % confidence interval +7.3 to +21.7) for atracurium (seven patients) and 11.1 min (95 % confidence interval −2.1 to 24.3 min) for vecuronium (nine patients).

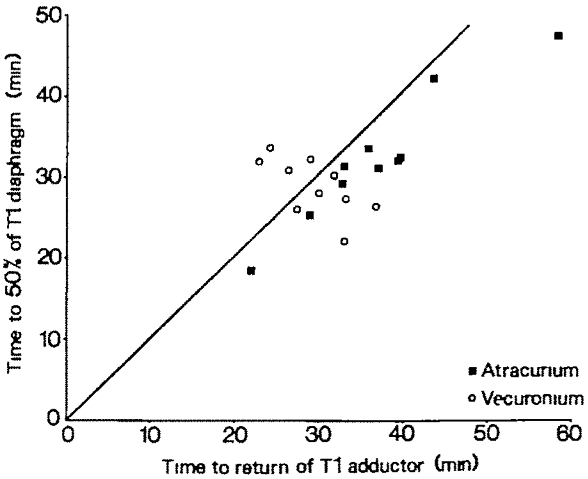


FIG. 5. Time to recovery of the first twitch of the train-of-four (TOF) to 50 % of its control height in the diaphragm is plotted against time to reappearance of the first twitch of the TOF of adductor pollicis. The line of identity is also displayed. ■ = Recovery after administration of atracurium 0.4–0.5 mg kg^{-1}; ○ = after vecuronium 0.08–0.1 mg kg^{-1}.

DISCUSSION

This study has investigated the relationship between adductor pollicis twitch and diaphragm twitch after administration of a neuromuscular blocking drug and was not intended to compare directly the pharmacological effects of atracurium with those of vecuronium.

In 10 patients following administration of atracurium, paralysis occurred in the diaphragm before adductor pollicis. During spontaneous recovery, all four twitches of the TOF appeared in the diaphragm in addition to 50 % recovery of $T1_D$ before there was any evidence of recovery in adductor pollicis. Thus evoked adductor pollicis twitch provides confirmation of the onset of paralysis in the diaphragm and of diaphragmatic recovery, but cannot be relied upon as implying paralysis of the diaphragm during operation. There was a very wide variation in recovery times, the time to reappearance of $T1_D$ usually being two-thirds of the time to reappearance of $T1_{AP}$.

After vecuronium, paralysis occurred in the diaphragm at the same time as or before that in adductor pollicis and the return of function in the diaphragm was more rapid than in adductor pollicis. However, the times to onset of recovery, as indicated by the reappearance of T1 in each muscle, were often similar, usually 20–30 min.

There were some problems associated with the methodology of this study which deserve discussion. The most important is the assumption that the transdiaphragmatic pressure generated by supramaximal phrenic stimulation is equivalent to, and thus comparable with, evoked adductor pollicis twitch. Both are direct measurements of the product of muscle action—the transdiaphragmatic pressure generated after phrenic stimulation is a mechanical measurement of the global diaphragm response and the strain gauge record of adductor pollicis twitch strength after ulnar nerve stimulation is a mechanical measurement of the response of the adductor pollicis muscle as a whole. Although the electromyograph (EMG) is often quoted as a quantitative measure of muscle activity this may be misleading. The different distances of each muscle fibre from the recording electrodes and the fact that these distances may vary with muscle contraction, imply that the EMG is not a direct measurement. This is true especially in the case of the diaphragm, where electrode apposition is difficult. In addition, the electrical signal does not necessarily reflect power output and there have been suggestions that diaphragmatic EMG may even increase whilst developed tension fails [12].

Only single twitch and TOF stimulation were used in this study, but physiological traffic in the phrenic nerve is tetanic in nature. Walts, Levin and Dillon [13] reported that recovery of tetanic stimulation in the forearm lagged behind recovery of single twitch.

The administration of suxamethonium to facilitate tracheal intubation is a common event. The drug under study was given at least 15–20 min afterwards so that residual effects from the depolarizing block, although undoubtably present, would be minimal. The background of inhalation anaesthesia was necessary to minimize the risk of awareness and enable surgery to continue while the equipment was applied. This undoubtedly contributed to the rapid onset of neuromuscular blockade.

The interpretation of tests of peripheral neuromuscular blockade and the extrapolation of this to other muscle groups has emanated from research including animal work, and studies in awake volunteers and patients following operation.

In dogs and in cats, Waud and Waud [14] investigated the action of tubocurarine on the diaphragm and on the anterior tibialis muscle. They reported that, in cats, an average of 10% (range 2.8–17.2%) more receptors needed to be blocked in the diaphragm than in the tibialis anterior to reduce the twitch response by 50%. In dogs there was less difference (0.6%, with 95% confidence limits −6.6 to +7.7%). The experimental procedure is too invasive for application in man as it involved dissection of muscle insertions in the diaphragm, but nonetheless the results do not suggest a margin of safety in the diaphragm.

In awake volunteers Cohen, Paulson and Elert [15] described the "respiratory saving" activity of tubocurarine, but noted that it was not a constant feature. Later work, however, suggested that there was little impairment of vital capacity and respiratory muscle power when grip strength was greatly reduced after tubocurarine and that recovery of peripheral muscles was more prolonged [4, 6, 13, 16] than that of diaphragm. Many of these studies may be criticized because the numbers involved were very small, commonly between four and six subjects, and because subclinical doses were used. Although the subjects involved were healthy and young, a very wide sensitivity to relaxants was reported, leading to the exclusion of some data from the results and conclusions [6, 13]. Positive aspects of this work include that the muscle tests were tetanic in nature. Walts, Levin and Dillon [13] correlated recovery of vital capacity and of maximum voluntary ventilation with the ability to sustain tetanus at 30 Hz in the adductor pollicis muscle.

In anaesthetized man, Bendixen and his fellow workers [17] suggested that inspiratory force was a more sensitive index of the recovery of the muscles of ventilation after the use of neuromuscular blocking drugs than was the ability to maintain ventilation. Wymore and Eisele [7] compared thumb twitch with the inspiratory force generated after airway occlusion at end expiration, and observed a wide range of sensitivities between different patients. Donati and co-workers have reported three studies [18–20] in which evoked tests of diaphragm (EMG) and adductor pollicis (mechanical twitch) have been compared during anaesthesia after administration of serial doses of blocking drugs in order to describe dose–response curves for each muscle. Recently, Chauvin, Lebrault and Duvaldestin [21] reported onset of paralysis and recovery in the diaphragm and adductor pollicis after administration of vecuronium, recording the mechanical twitch of each muscle after bilateral phrenic nerve and unilateral ulnar nerve stimulation. They reported earlier onset of paralysis in the diaphragm and earlier and more extensive recovery than in adductor pollicis.

The results of the present study may have the following implications when applied to anaesthetic practice: First, monitoring of neuromuscular blockade in adductor pollicis is useful in determining when tracheal intubation may be performed without the risk of coughing or of muscle movement. Second, during upper abdominal surgery, when atracurium is used for neuromuscular blockade, monitoring of adductor pollicis twitch is not sufficiently sensitive to maintain the diaphragm paralysed. However, atracurium may be a suitable drug if there is concern regarding recovery in the diaphragm, in this case, return of function in adductor pollicis may be used to confirm diaphragmatic recovery. It also suggests that atracurium is appropriate for operations on the periphery when diaphragmatic paralysis is not necessary. The wide variation in the duration of neuromuscular blockade after atracurium implies that monitoring of neuromuscular blockade is particularly important so that individual responses to a dose can be assessed. Finally, vecuronium may produce a more predictable duration of blockade both in adductor pollicis and in the diaphragm. It would seem, therefore, that this drug is preferable for upper abdominal surgery.

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POTENCY OF ATRACURIUM AND VECURONIUM AT THE DIAPHRAGM AND THE ADDUCTOR POLLICIS MUSCLE

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In awake individuals, respiratory muscles are known to be relatively resistant to neuromuscular blocking drugs when compared with peripheral muscle [1–3]. In anaesthetized patients, the dose of tubocurarine causing depression of inspiratory force was found to be 1.8–1.9 times as large as that blocking the adductor pollicis [4]. Using phrenic nerve stimulation, it was found that twice as much pancuronium was required to produce blockade at the diaphragm comparable to that at the adductor pollicis [5].

For practical reasons, neuromuscular blockade is monitored routinely by stimulating the ulnar nerve and observing the response of the adductor pollicis muscle. Thus it is important to measure the relationship between adductor pollicis blockade and diaphragm blockade produced by neuromuscular blocking drugs used in clinical practice.

In animals, the degree of diaphragm resistance is not necessarily the same for all neuromuscular blockers [6], so that the results obtained with tubocurarine and pancuronium do not necessarily apply to atracurium and vecuronium. The purpose of this study was to assess the relative potencies of these newer agents at the adductor pollicis and the diaphragm.

SUMMARY

Train-of-four stimulation was applied to the ulnar and phrenic nerves in 18 adult patients anaesthetized with nitrous oxide and halothane in oxygen. The response of the adductor pollicis and the diaphragm were measured. Incremental doses of atracurium and vecuronium were given, with an infusion to replace drug lost by elimination or distribution. The mean (SEM) doses of atracurium associated with 50% and 90% depression of response to the first stimulation in the train-of-four (ED_{50} and ED_{90}) were 90 (9) and 133 (10) µg kg^{-1} at the adductor pollicis, and 130 (9) and 245 (17) µg kg^{-1} at the diaphragm, respectively. The mean (SEM) ED_{50} and ED_{90} of vecuronium were 25 (2) and 38 (4) µg kg^{-1} at the adductor pollicis and 34 (3) and 58 (5) µg kg^{-1}at the diaphragm, respectively. The mean (SEM) ED_{50} ratios were 1.56 (0.16) for atracurium and 1.47 (0.16) for vecuronium. ED_{90} ratios were 1.93 (0.29) and 1.55 (0.17) for atracurium and vecuronium, respectively. It is concluded that both atracurium and vecuronium exhibit a similar degree of sparing of the diaphragm.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent obtained from all subjects. Eighteen patients scheduled to undergo peripheral surgical procedures were entered to the study. They were devoid of neuromuscular, renal or hepatic disease, and were receiving no chronic medication. Premedication was atropine 0.007 mg kg^{-1} and morphine 0.1 mg kg^{-1} 1 h before the scheduled start of the procedure. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1}, followed by 70% nitrous oxide and halothane in oxygen by face mask until tracheal intubation was accomplished without the use of neuromuscular blocking drugs. After tracheal intubation, the inspired halothane concentration was set at 0.75% and the lungs were ventilated using a Mapleson D system with a fresh gas flow of 70 ml kg^{-1} min^{-1}.

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The method described by Donati, Antzaka and Bevan [5] to measure force of contraction of adductor pollicis and the diaphragmatic electromyogram (EMG) was used. Supramaximal stimulation with square pulses of 0.2 ms duration was applied to the ulnar nerve at the elbow. Four pulses were delivered at a frequency of 2 Hz (train-of-four) every 12 s. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis muscle was measured with a force displacement transducer (Grass FT-10) and displayed on a chart recorder. Train-of-four stimulation was applied also to the right phrenic nerve in the neck at intervals of no less than 12 s. The diaphragmatic EMG signal was recorded through three surface electrodes placed in the 8th intercostal space on the right. The signal was passed through an amplifier with a 3–300 Hz bandwith and displayed on a storage oscilloscope. The intensity of the diaphragmatic response was taken as the height of the deflection of the EMG signal. To minimize interference with ventilation and the conduct of surgery, the frequency of phrenic nerve stimulation was limited. After three to five control measurements, the phrenic nerve was stimulated only when adductor pollicis twitch height was stable, at which time two or three diaphragmatic measurements were made over 1–2 min.

After control measurements had been obtained, cumulative doses of atracurium or vecuronium were administered. An initial dose of atracurium 0.1 mg kg^{-1} was given and, when both adductor pollicis and diaphragm responses were stable, increments of 0.05 mg kg^{-1} were administered until both the diaphragmatic and adductor pollicis responses to the first stimulation of the train-of-four were depressed by more than 90%. In the case of vecuronium, an initial bolus of 0.02 mg kg^{-1} was given, followed by increments of 0.01 mg kg^{-1}.

To allow for the relatively rapid elimination of atracurium and vecuronium, an infusion of the drug was commenced when a stable response was seen and the rate of infusion was increased after each succeeding set of measurements. The infusion rate was based on known values of ED$_{95}$ and the dose required to maintain that block constant. For atracurium, the infusion rate to maintain 95% block under halothane anaesthesia is 0.36–0.50 mg kg^{-1} h^{-1} [7–9], approximately three times as much as the ED$_{95}$, which is 0.111–0.26 mg kg^{-1} [9–11]. For vecuronium, the infusion rate to maintain 95% blockade is 0.06–0.075 mg kg^{-1} h^{-1} [12, 13], which is approximately twice the ED$_{95}$ dose under halothane anaesthesia [14, 15]. Thus the hourly rate of infusion was set at three times the dose of atracurium already given, and at twice the dose of vecuronium already given.

For example, when maximum blockade from the initial dose of atracurium 0.1 mg kg^{-1} was achieved, a bolus dose of 0.05 mg kg^{-1} was given. At the same time, an infusion of atracurium was started, at a rate equal to three times the initial dose per hour; that is 0.3 mg kg h^{-1}. When the second dose produced its maximum effect, a third dose was administered, and the infusion rate was increased to 0.45 mg kg^{-1} h^{-1}—three times the sum of the first two doses, per hour. Subsequently, the infusion rate was increased after each of the successive doses. In calculating dose–response relationships, only the total of the bolus doses was considered, because the infusion compensated only for drug lost by elimination or redistribution. This cumulative dose-with-infusion method has been shown to yield dose–response relationships of vecuronium and atracurium which are undistinguishable from those obtained with single-dose methods [16].

First twitch responses for both muscles were compared with their respective control values to construct cumulative dose–response curves. A regression line, obtained by least squares analysis for each patient, was plotted on probit-log paper, and mean dose–response curves were calculated. Effective doses for 50% and 90% blockade (ED$_{50}$ and ED$_{90}$) were derived from the curves for each muscle, and the potency ratios between the diaphragm and the adductor pollicis were calculated. Potency ratios for atracurium and vecuronium were compared using Student's t test. The results are presented as mean values with SEM.

RESULTS

There were no significant differences between the two groups of patients in age, weight or sex distribution (table I).

TABLE I. *Sex ratio and mean (SEM) values for age and weight in the two patient groups*

	Sex (M:F)	Age (yr)	Weight (kg)
Atracurium ($n = 9$)	5:4	41 (3.6)	72 (4.7)
Vecuronium ($n = 9$)	7:2	48 (4.5)	70 (2.8)

TABLE II. *Data obtained at the adductor pollicis and diaphragm in a patient receiving atracurium*

	Time (min)											
	0	4	6	10	12	15	17	20	22	25	27	30
Atracurium dose (mg kg^{-1})	0.1		0.05		0.05		0.05		0.05		0.05	
Cumulative dose (mg kg^{-1})	0.1		0.15		0.20		0.25		0.30		0.35	
Infusion rate (mg kg^{-1} h^{-1})		0.3		0.45		0.60		0.75		0.90		1.05
Adductor pollicis T1 (%)	100	85	80	35	33	7	6	2	2			
T4/T1 (%)	100	55	48	11	10	0	0	0	0			
Diaphragm T1 (%)	100	98	98	76	77	40	38	21	23	15	13	8
T4/T1 (%)	100	70	67	46	45	17	15	0	0	0	0	0

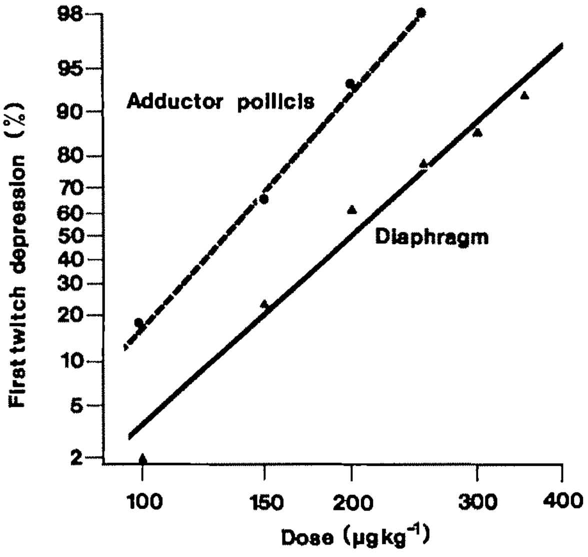

FIG. 1 Adductor pollicis and diaphragm responses *v.* dose of atracurium for the patient shown in table II.

The mean (SEM) time interval between injection of the first dose and maximum blockade of adductor pollicis was 5.5 (0.2) min for atracurium and 4.5 (0.1) min for vecuronium. For subsequent doses, the intervals were 3.6 (0.2) and 2.8 (0.6) min, respectively. When the adductor pollicis was stable, diaphragmatic recordings were made two or three times and were found also to be stable. When the response of the adductor pollicis disappeared, the response of the diaphragm was tested at the same intervals. A mean of five incremental doses was used for each patient (range 4–8), and the study was completed within 25–30 min. An example of an individual patient's recording is shown in table II. The corresponding dose–response curve is shown in figure 1.

Approximately 1.5–2 times as much atracurium or vecuronium was needed for intense degrees of blockade of the diaphragm compared with that required for adductor pollicis. For atracurium, the diaphragm dose–response relationship was significantly flatter than that of the adductor pollicis ($P = 0.002$). Thus the discrepancy between adductor pollicis and diaphragm was greater at more intense degrees of blockade (fig. 2). The two curves did not diverge significantly from parallel in the case of vecuronium (fig. 3). Although the ratio of diaphragm to adductor

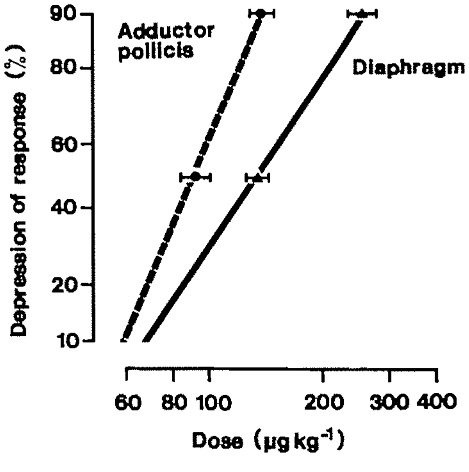

FIG. 2 Mean cumulative dose–response curve for atracurium, showing per cent depression of response to first stimulus in train-of-four (probit scale) *v.* dose (log scale), for the adductor pollicis twitch tension and diaphragm electromyogram.

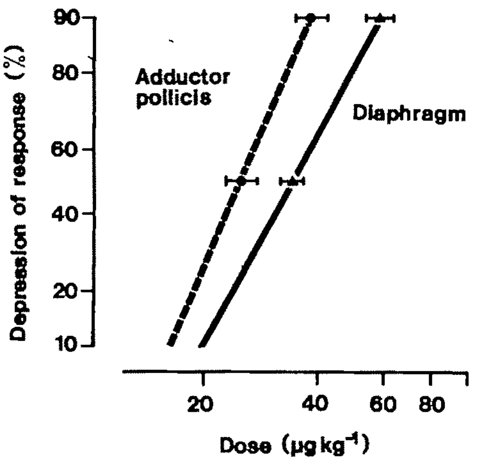

FIG. 3 Mean cumulative dose–response curve for vecuronium, showing per cent depression of response to first stimulus in train-of-four (probit scale) *v*. dose (log scale), for the adductor pollicis twitch tension and diaphragm electromyogram.

TABLE III. *Adductor pollicis (AP) and diaphragm (D) ED_{50} and ED_{90} (SEM) for first twitch response. Mean ratio (SEM) of diaphragm to adductor pollicis response from individual patient dose–response curves*

	Atracurium	Vecuronium
ED_{50}		
AP (µg kg^{-1})	90 (9)	25 (2)
D (µg kg^{-1})	130 (9)	34 (3)
Ratio D:AP	1.56 (0.16)	1.47 (0.16)
ED_{90}		
AP (µg kg^{-1})	133 (1.0)	38 (4)
D (µg kg^{-1})	245 (17)	58 (5)
Ratio D:AP	1.93 (0.29)	1.55 (0.17)

pollicis ED_{90} was greater in the case of atracurium (1.93 *v*. 1.55), this difference was not significant (table III). At 90 % twitch depression of adductor pollicis, mean (SEM) diaphragmatic EMG depression was 53 (6) % with atracurium, and 59 (9) % with vecuronium.

Train-of-four fade was observed at both the diaphragm and the adductor pollicis muscles (table II). The degree of fade took much longer to stabilize than did first degree depression and dose–response relationships for train-of-four fade could not be obtained.

DISCUSSION

This study demonstrated that atracurium and vecuronium exhibited approximately the same degree of sparing of the diaphragm. At 90 % adductor pollicis blockade, which corresponds to an adequate degree of surgical relaxation, the diaphragm was depressed by 53 % with atracurium and 59 % with vecuronium. However, the data suggest that the effect of these two drugs on the diaphragm might be slightly different, because the slope of the dose–response relationship was significantly less for atracurium compared with vecuronium. As a result, the ratio of diaphragm ED_{90} to adductor pollicis ED_{90} was greater for atracurium, although not significantly.

Cumulative dose–response techniques are a powerful tool for comparing the potency of a neuromuscular blocking drug at two muscles. Many points can be obtained in the same individual, so that the uncertain treatment of 0 and 100 % can be avoided, comparisons between muscles of widely different sensitivities can be made in the same individual, and fewer patients are required to produce statistically significant results. For the longer acting blocking agents, there is no difference between dose–response curves obtained with either the cumulative or the single-dose method [17], probably because little elimination of the drug occurs during the study period. However, this technique may not apply to atracurium [18], or vecuronium [19, 20] because of their short duration of action. It follows that a technique which involves the administration of additional drug to compensate for losses produced by redistribution or elimination would improve the accuracy of cumulative dose results. Our results suggest that this is the case for atracurium and vecuronium [16].

The force of contraction of the adductor pollicis was measured because it is the standard which has been used in studies describing the potency of neuromuscular blocking drugs; no accepted standard exists regarding electrode placement and electronic integration of the adductor pollicis EMG [21]. In spite of this, depression of EMG and twitch tension are almost identical, at least with atracurium [21–22]. In contrast, the measurement of diaphragmatic twitch tension is difficult, if not impossible, to perform; ideally, a resting tension is required. Even with a closed airway, a truly isometric contraction of the diaphragm cannot be obtained, because it changes the geometry of the chest wall and abdomen. Transdiaphragmatic pressure, which is the most common method of measuring diaphragmatic activity, preferably requires both phrenic nerves to be stimulated. For these reasons, the EMG was preferred as a measure of diaphragmatic activity, and twitch tension of the thumb was chosen as a measure of adductor pollicis activity.

The difference in sensitivity between the diaphragm and peripheral muscles may not be the same for all neuromuscular blocking drugs. For example, in the guineapig the ratio of latissimus dorsi to diaphragm sensitivity was 2 for tubocurarine and 4 for dimethyl tubocurarine [6]. In this study, the adductor pollicis : diaphragm sensitivity ratio at 90% block was 1.55 for vecuronium and 1.93 for atracurium, but the difference was not statistically significant, largely because of the great dispersion of values obtained with atracurium. Thus the data are insufficient to demonstrate a different degree of a diaphragm sparing between the two drugs. By the same methodology as in the present study, the adductor pollicis : diaphragm sensitivity ratio was found to be 2.14 for pancuronium [5]. However, comparisons between studies should be made with caution, and it is unjustifiable to conclude that there is any difference in the degree of diaphragmatic sparing between atracurium, vecuronium and pancuronium.

Our results agree with those obtained with other techniques on the ventilatory effects of neuromuscular blockers. After vecuronium 0.1 mg kg^{-1} or atracurium 0.6 mg kg^{-1} the adductor pollicis recovers after the mechanical strength of the diaphragm has been regained [23, 24]. The dose of tubocurarine required to decrease inspiratory pressure by 90% was 1.91 times that needed to block evoked adductor pollicis twitch height with 1 Hz stimulation [4]. In volunteers, vital capacity was affected much less by tubocurarine than was grip strength [1–3, 25]. Although the techniques used in these studies were not the same as those used here, the results all point to some degree of sparing of the muscles of ventilation.

Total relaxation of all muscles does not occur unless the diaphragm is paralysed also, and this requires 1.5–2 times that causing comparable blockade of the adductor pollicis. If inter-individual variability is taken into consideration, it is not surprising to find that doses as great as three times the ED$_{95}$ of a blocking agent often do not produce perfect conditions for tracheal intubation [26]. Thus data on diaphragmatic sensitivity to neuromuscular blockers may be important in determining intubating doses.

To assess recovery, the use of a sensitive muscle such as the adductor pollicis has definite advantages. The intercostal muscles and the upper airway muscles are probably more sensitive than the diaphragm [27, 28] and their sensitivity may be closer to that of the adductor pollicis. Furthermore, overestimation of the degree of train-of-four recovery occurs frequently in the clinical setting [29]. It follows that monitoring a relatively sensitive muscle is probably safer than monitoring a more resistant muscle, because residual paralysis is much more likely to be detected with the former. Thus diaphragm sparing probably increases the safety of monitoring of adductor pollicis.

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EFFECT OF SUXAMETHONIUM GIVEN DURING RECOVERY FROM ATRACURIUM

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Summary

Suxamethonium was given in varying doses when twitch response had returned to 50% of control following the administration of atracurium in anaesthetized patients. Small doses of suxamethonium produced antagonism, enhancement of the block, or a combination showing a biphasic response. A dose of 3 mg kg⁻¹ was needed to produce consistently 100% block of the twitch. The subsequent recovery rate for T1 was as fast as that seen normally after suxamethonium and was not enhanced by neostigmine.

At the end of an abdominal operation, muscle relaxation may be inadequate and a transient increase in block may be needed to facilitate closure. Suxamethonium is the only agent of short duration available currently [1] and has been used in these circumstances. Whilst interactions with long acting competitive agents have been described [2–5], there are no descriptions of its effect on recovery from the block produced by atracurium. This study was designed to assess the effects of increasing doses of suxamethonium on the recovery of block produced by atracurium and on the subsequent interaction with neostigmine.

PATIENTS AND METHODS

Thirty-eight patients (18–70 yr, 45–110 kg) undergoing elective surgical procedures were studied after they had given informed consent. No patient who had received aminoglycoside antibiotics was studied. The study was approved by the local Ethics Committee.

Diazepam 10–20 mg and metoclopramide 10 mg were given by mouth 1 h before anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2 – 4 μg kg^{-1}. Anaesthesia was maintained with 66% nitrous oxide and 0.5% enflurane in oxygen supplemented by additional doses of fentanyl and thiopentone as required. End-tidal carbon dioxide tension was maintained at 4–5 kPa.

The integrated, rectified and gated electromyographic response of the hypothenar muscles was recorded in response to supramaximal train-of-four stimuli delivered to the ulnar nerve at 20-s intervals using a Datex Relaxograph. Control records were obtained after induction of anaesthesia but before a block was produced with an initial dose of atracurium 0.4 mg kg^{-1}.

The first twitch (T1) of the train-of-four was allowed to recover to 50% of the control value in 22 patients. Suxamethonium 0.25, 0.5, 1, 1.5, 2 or 3 mg kg^{-1} was given i.v. and the subsequent course of paralysis noted. When the first twitch had recovered to 100% (in some patients in whom the train-of-four ratio remained less than 0.6 after several minutes of monitoring), the additional effect of neostigmine 35 μg kg^{-1} was noted (table I).

In order to provide comparative recovery data, three further groups were studied: atracurium 0.4 mg kg^{-1} with spontaneous recovery, atracurium 0.4 mg kg^{-1} with antagonism by neostigmine 35 μg kg^{-1} at T1 10–25%; and spontaneous recovery of suxamethonium 1.5 mg kg^{-1} without any preceding atracurium.

In order to mimic a possible clinical situation, in a further four patients the initial dose of atracurium was allowed to recover to 50% T1 and suxamethonium 3 mg kg^{-1} was given in the same manner as in the first study, but neostigmine 35 μg

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TABLE I. *Study groups. *Suxamethonium administered at 50% T1 recovery from a 0.4-mg kg^{-1} atracurium block*

n	Atracurium (mg kg^{-1})	Suxamethonium (mg kg^{-1})	Neostigmine (µg kg^{-1})
1	0.4	0.25 at 50% T1*	±35 at 100% T1
4	0.4	0.5 at 50% T1	±35 at 100% T1
4	0.4	1.0 at 50% T1	±35 at 100% T1
3	0.4	1.5 at 50% T1	±35 at 100% T1
6	0.4	2.0 at 50% T1	±35 at 100% T1
4	0.4	3.0 at 50% T1	±35 at 100% T1
4	0.4	3.0 at 50% T1	+35 at 25% T1
4	0.4	—	—
4	0.4	—	+35 at 10–25% T1
4	—	1.5	—

TABLE II. *Effect of suxamethonium on a recovering (50% T1) atracurium block. *Four patients received neostigmine at 25% T1 after suxamethonium (see table III). **A 50% change in block represents 100% block of T1*

Dose of Sux. (mg kg^{-1})	n	No. with biphasic response	Mean (SD) change in block (%)	T1 100% block time (min)
0.25	1	0	−10	
0.5	4	2	−1.25 (10.3)	
1.0	4	2	−1 (12.5)	
1.5	3	2	34 (17.7)	
2.0	6	4	40.5 (13.5)	
3.0	8*	3	50**	8

kg^{-1} was given when the T1 had returned again to 25%. The response to suxamethonium 3 mg kg^{-1} in this study ($n = 4$) is included in table II with the results of the first study of the effect of suxamethonium on a recovering atracurium block ($n = 4$) so that overall, $n = 8$. However, the recovery data for these two groups were different and are tabulated separately (table III).

TABLE III. *Reversal data (mean (SD)). AS = Suxamethonium 3 mg kg^{-1} administered at a 50% T1 atracurium recovery; AS+N = neostigmine administered at 25% T1 recovery of AS block; S = suxamethonium 1.5 mg kg^{-1}; A = atracurium 0.4 mg kg^{-1}; A+N = neostigmine reversed (at 10–25% T1) atracurium blockade*

Group	n	25–75% recovery (min)	5–95% recovery (min)
AS	4	2.75 (0.28)	8.25 (0.95)
AS+N	4	7.25 (3.6)	12.3 (5.9)
S	4	3 (0)	7.75 (0.5)
A	4	13.1 (1.8)	38.3 (7.6)
A+N	4	4.5 (0.57)	14.5 (1.73)

RESULTS

Giving suxamethonium when T1 had recovered to 50% after the administration of atracurium produced no effect on the block, a mild increase in recovery rate, an enhancement of the block, or a biphasic response. Figure 1 shows a biphasic response in which there was an initial reversal, followed by the development of full block and later recovery. There were marked variations between patients for each dose of suxamethonium, but the net effect of the lower doses was to antagonize the block and of higher doses to enhance it. Only with suxamethonium 3 mg kg^{-1} was it possible consistently to produce a complete block: this lasted some 8 min before recovery (table II).

When atracurium was given alone the mean recovery index (25–75% T1 recovery) was 13.1 min, and when neostigmine was given at 10–25% T1 this time was shortened, on average to 4.5 min. When suxamethonium 3 mg kg^{-1} was given at 50% T1 recovery after atracurium, the recovery index following the period of 100% block was

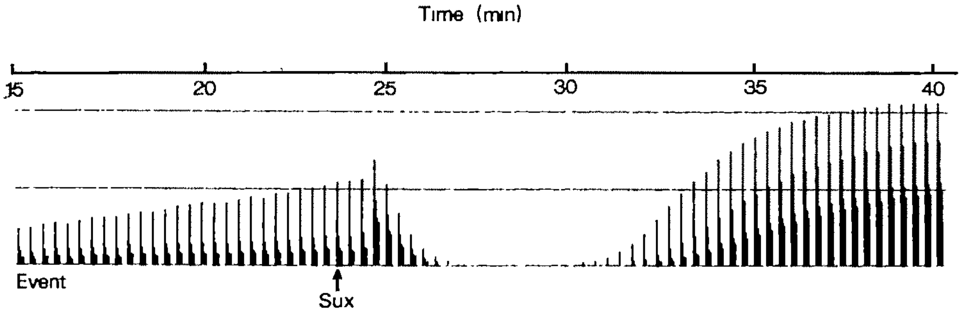

FIG 1. Effect of suxamethonium on a recovering atracurium block. Suxamethonium 2 mg kg^{-1} (Sux.) was administered at 50% T1 recovery from an atracurium 0.4 mg kg^{-1} blockade. Subsequent biphasic response followed by a brief period of 100% T1 block and a rapid recovery.

2.75 min and the 5–95% recovery time was 8.25 min. These times are very similar to those recorded following a spontaneous suxamethonium 1.5 mg kg^{-1} recovery (3 and 7.75 min, respectively). However, fade always persisted following the block induced by suxamethonium after atracurium, despite the rapid recovery of T1; but this fade was always reversed when neostigmine was administered at 100% T1 recovery (table III).

When suxamethonium 3 mg kg^{-1} was administered at a 50% T1 recovery from atracurium, and neostigmine was administered subsequently at the earlier stage of 25% T1 of this combination block, fade was reversed. The mean recovery index, however, was prolonged to 7.25 min and in one patient neostigmine transiently increased the block by 10%, prolonging the 5–95% recovery time to 19 min. Thus the fastest recovery times were observed after suxamethonium 1.5 mg kg^{-1} alone, or during the recovery stage of a suxamethonium 3 mg kg^{-1}-potentiated atracurium block. While the addition of neostigmine reversed fade when administered at 100% T1 after the combination block, neostigmine slowed recovery of this block when administered at the earlier stage of recovery (T1 25%).

Suxamethonium given after atracurium did not produce muscle fasciculations.

DISCUSSION

This study was designed to mimic a clinical problem. The blockade produced by atracurium was allowed to wear off to a point at which T1 had recovered to 50% and where all four responses to train-of-four stimulation were apparent. This level of recovery is usually too great to allow closure of the abdomen without deep general anaesthesia, and the anaesthetists should intensify the block. It was common to use a small dose of suxamethonium for this rather than give an increment of a long acting competitive blocker.

Our results show that small doses of suxamethonium may antagonize the partial block seen during recovery from atracurium, but that larger doses usually enhance the block. The subsequent pattern of recovery of a combination block is faster than that seen with atracurium alone or when antagonized by neostigmine. However, during the recovery of a combination block, fade of the train-of-four response is seen. Similar results have been reported with the interaction of suxamethonium with longer acting competitive blocking drugs [2–5]. Young [4] and Walts [2] demonstrated similar patterns of dose-related effect with tubocurarine, as did Katz for pancuronium [3]. The biphasic pattern has been described by Walts [2] and in more detail by Buzello and his colleagues [5]. This last study demonstrated that, with a constant dose of suxamethonium 0.5 mg kg^{-1}, the proportional relationship between reversal and subsequent increase of blockade depends on the stage of recovery from non-depolarizing neuromuscular blockade at the time of administration of suxamethonium. Young [4] reported similar findings.

What are the mechanisms which produce these interactions? The traditional view would be that atracurium produces mainly a competitive block of the post-synaptic receptors. Such a block may be overcome by increasing the concentration of agonist usually, in clinical practice, by the administration of neostigmine. However, suxamethonium also acts as an agonist and interacts with the post-synaptic receptors, leading to the opening of ionic channels and depolarization of the membrane. In turn, this may initiate a muscle action potential and contraction. If the amount of suxamethonium is too great, depolarization is maintained and the muscle membrane becomes inexcitable. Hence small doses may act as antagonists, but larger ones produce a block as the depolarization develops.

We still need to explain why the recovery index is quicker during recovery from the combination block, why neostigmine slows it and why fade of the train-of-four response persists. Again, the traditional view of block may provide an explanation. The enhanced recovery index by itself may be misleading. It is likely that what we are observing is a simple competitive displacement by the law of mass action at the post-junctional receptor: the dose–response curve of suxamethonium is shifted to the right because of the presence of atracurium molecules on the receptor.

It appears from Buzello's study [5] that, when suxamethonium is administered during a pancuronium recovery phase, 100% T1 recovery was not achieved at 30 min following suxamethonium when administered at 25% or 75% recovery of T1. In our study every patient had recovered to 100% T1 from a combination block (suxamethonium 3 mg kg^{-1}) within 20 min of administration of suxamethonium. This observation supports our hypothesis. As suxamethonium is catabolized and the local concentration declines at the end-plate, the post-junctional receptors may be occupied by the longer acting pancuronium molecules, which are eliminated more slowly. This does not occur with atracurium, which has intermediate duration of action, because elimination is occurring more rapidly than with pancuronium during the time that suxamethonium is being hydrolysed. Thus the fast recovery index reflects the fact that most of the block is produced by suxamethonium. The fact that neostigmine slowed recovery after suxamethonium may be a result of its effect on plasma, in addition to true cholinesterase, thereby delaying the breakdown of suxamethonium.

Fade is now believed to result either from a block of pre-junctional acetylcholine receptors by competitive drugs or from a use-dependent occlusion of the post-junctional ion channel [6]. However, the latter hypothesis ignores the findings of Hutter [7] and Otsuka and colleagues [8] that tubocurarine-induced fade is associated with diminished release of acetylcholine and, certainly, the evidence for drugs used in clinical circumstances favours the first of these two mechanisms. The fade demonstrable during the recovery from suxamethonium following atracurium is accounted for most probably by the residual pre-junctional action of atracurium. It may result from development of a phase 2 block [9] by suxamethonium, but this would seem unlikely because of the rapid recovery time. Furthermore, neostigmine did not shorten the recovery time, and on one occasion actually increased block, adding substance to the hypothesis that a depolarizing block is present. In any event, all these explanations are speculative, especially with the difficulties inherent in comparing the evoked electromyographic responses demonstrable in man with the precise studies now possible in the laboratory. A detailed study of the interactions would presumably need voltage [10] and patch clamp studies to ascertain which effects result from interaction with acetylcholine receptors on the muscle and which from effects on receptors on the nerve terminals.

The data generated by the indirectly evoked EMG should be used with some understanding of its limitations as a predictor of mechanical response. Although Carter and colleagues [11] found a good correlation between the two methods of measurement for both twitch height and train-of-four ratio (correlation coefficients 0.93 and 0.97, respectively), Kopman [12] found that the simultaneously evoked (hypothenar) EMG and MMG did not give identical information. The regression line for the T1:Tc (twitch depression/control twitch) ratio was parallel to the line of identity, but showed an absolute offset of 15%. Furthermore, the EMG baseline may drift with time as a result of a number of possible factors and return to T1:Tc control values does not always occur.

The Datex EMG was chosen in this study because it is a compact and convenient tool, providing information on the nature of the response to be expected from certain drug interactions, rather than a precise quantification of effect. Where significant baseline drift was observed ($T1:Tc < 0.85$) the data were excluded from the study. These limitations do not detract from our conclusions.

Although we did not see prolonged block when suxamethonium 3 mg kg^{-1} was given after recovery from atracurium to a 50% T1 level, we would not recommend giving such a dose to enhance neuromuscular blockade in clinical practice unless a peripheral nerve stimulator were used to monitor the degree and duration of block. If such a technique is used, neostigmine appears not to accelerate the subsequent recovery and should not be used. It is important to remember that we gave the suxamethonium at 50% T1, at which time all four responses to train-of-four stimulation were present. An alternative clinical solution would be to increase the block with a small increment of atracurium. The intensity, duration and subsequent recovery of the block would then depend on the size of dose used.

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PHARMACOKINETICS OF DROPERIDOL IN SURGICAL PATIENTS UNDER DIFFERENT CONDITIONS OF ANAESTHESIA

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SUMMARY

The pharmacokinetics of droperidol were studied in 42 surgical patients using doses of 5, 10 and 15 mg i.v., in association with neuroleptanalgesia or volatile anaesthetics. Plasma concentrations of droperidol were measured by radioimmunoassay. During neuroleptanalgesia, droperidol kinetics were linear over the dose range tested: the overall mean elimination half-life was 127 min, Vd^{ss} *103 litre and the plasma clearance 732 ml* min^{-1}*. The kinetics of droperidol were similar under neuroleptanalgesia and under anaesthesia with halothane or enflurane. There was no significant correlation between the volume of distribution or clearance with age (14–65 yr) or body weight (48–90 kg).*

Droperidol is a butyrophenone with neuroleptic properties used to supplement anaesthesia. It has pronounced antiemetic effects. Droperidol is often combined with volatile anaesthetics during balanced anaesthesia, or with the potent narcotic analgesics fentanyl or alfentanil in neuroleptanalgesia.

Data on the pharmacokinetics of droperidol in man are scarce. Cressman, Plostnieks and Johnson [1], performed a preliminary pharmacokinetic study in healthy, non-anaesthetized volunteers after an i.v. dose of 5 mg of ^{3}H-labelled droperidol. They determined the concentrations of droperidol by a radioassay after thin-layer chromatographic separation of droperidol. An elimination half-life of 134 min was obtained but no values of the clearance or the volumes of distribution were reported. More recently, Fischler and colleagues [2] studied the kinetics of droperidol using a specific radioimmunoassay method after an i.v. bolus injection of 150 μg kg^{-1} in 10 anaesthetized patients.

In the present study, the knowledge on the pharmacokinetics of droperidol was extended. The linearity of the kinetics of droperidol i.v. was determined using doses of 5, 10 and 15 mg, and the possibility that volatile anaesthetics alter the kinetics of droperidol was also investigated. Because of the large patient population included, age and body weight were studied as possible factors influencing the variation in droperidol disposition.

PATIENTS AND METHODS

Forty-two patients (ASA grades I–II) scheduled to undergo elective abdominal, gynaecological or orthopaedic surgery participated after giving informed consent. Duration of surgery was at least 60 min. None of the patients had any significant hepatic or renal impairment. Individuals addicted to alcohol or drugs were excluded.

All patients were premedicated with diazepam 10 mg by mouth on the evening before surgery and 10 mg i.m. 1 h before surgery. Atropine 0.5 mg i.v. was followed by alcuronium 2 mg, diazepam 5 mg, hexobarbitone 3 mg kg^{-1} and 50% nitrous oxide in oxygen for 2–3 min. Suxamethonium 1 mg kg^{-1} was used to facilitate tracheal intubation.

Patients were randomly assigned to five groups. Patients of groups 1, 2 and 3 received a single dose of droperidol 5, 10 and 15 mg i.v. respectively,

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TABLE I. *Values of C_i and λ_i in the bi- and triexponential equations fitting the individual droperidol plasma concentrations*

Patient No.	C_1 (ng ml^{-1})	C_2 (ng ml^{-1})	C_3 (ng ml^{-1})	λ_1 (min^{-1})	λ_2 (min^{-1})	λ_3 (min^{-1})
Droperidol 5 mg						
1	375	40	—	0.527	0.0086	—
2	361	47	—	0.243	0.0068	—
3	1626	73	36	0.45	0.051	0.0068
4	66	27	—	0.254	0.0050	—
5	151	22	—	0.119	0.0053	—
6	505	24	14	0.48	0.037	0.0024
7	84	68	—	0.165	0.0067	—
8	451	40	31	0.32	0.035	0.0053
9	329	40	—	0.198	0.0062	—
10	251	37	—	0.248	0.0054	—
Droperidol 10 mg						
1	950	106	29	0.66	0.021	0.0036
2	1276	81	49	0.68	0.039	0.0049
3	11232	179	70	0.89	0.071	0.0071
4	770	115	65	0.27	0.035	0.0041
5	1967	132	—	0.282	0.0080	—
6	918	148	71	0.74	0.088	0 0064
7	351	116	—	0.149	0.0078	—
8	116	30	—	0.139	0.0061	—
9	436	97	—	0.345	0.0071	—
10	470	63	49	0.41	0.024	0.0040
Droperidol 15 mg						
1	489	128	—	0.158	0.0067	—
2	271	92	—	0.070	0.0050	—
3	2668	112	62	0.59	0.025	0.0053
4	2244	121	—	0.319	0.0055	—
5	257	127	—	0.099	0.0072	—
6	360	139	—	0.290	0.0071	—
7	2607	125	98	1.04	0.081	0.0057
8	176	107	—	0.242	0.0065	—
9	252	143	—	0.204	0.0068	—
10	345	70	—	0.525	0.0093	—
Halothane						
1	548	332	45	0.40	0.040	0.0044
2	1700	67	29	0.79	0.050	0.0050
3	1598	94	33	1.17	0.045	0.0051
4	262	54	28	0.79	0.040	0.0042
5	619	80	22	0.66	0.023	0.0040
6	3611	134	44	0.94	0.054	0.0056
Enflurane						
1	434	73	—	0.224	0.0072	—
2	118	68	—	0.067	0.0076	—
3	2054	44	34	1.07	0.052	0.0052
4	1016	71	40	0.83	0.065	0.0065
5	518	67	31	0.33	0.040	0.0043
6	1074	80	25	0.90	0.032	0.0046

together with fentanyl 4 μg kg^{-1} i.v. Artificial ventilation with a mixture of 60% nitrous oxide in oxygen was used. Supplementary doses of fentanyl 0.1–0.2 mg and alcuronium 3 mg were added when necessary. Patient groups 4 and 5 received droperidol 10 mg i.v. only but, initially, ventilation was with volatile anaesthetics: 1.5 vol% halothane or 2 vol% enflurane in nitrous oxide–oxygen. Ten minutes later, the halothane and enflurane concentrations were reduced to 1 and 1.5 vol%, respectively. Heparinized 3-ml venous blood samples were drawn from the contralateral arm in all patients, before administration of drugs and at 1, 3, 6, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min after administration. Blood samples were centrifuged and plasma was stored at −20 °C until required for assay.

Radioimmunoassay

Droperidol plasma concentrations were measured by a radioimmunoassay kit for benperidol (Janssen Life Sciences Products, Beerse, Belgium), because of the better radiochemical stability of ^{3}H-benperidol. The assay can be used for the determination of droperidol because of the favourable cross-reaction between both analogues, and metabolites of droperidol do not interfere. The method has been described in detail in the Appendix of the paper by Fischler and colleagues [2].

All plasma samples were measured in duplicate. Intra-assay variability between duplicates was 2.8 (0.1)%. Inter-assay variation was 12.3% and 13.9% for droperidol concentrations of 10 ng ml^{-1} and 1 ng ml^{-1}, respectively. Specific and non-specific binding were 44.2 (0.9)% and 1.9 (0.3)%, respectively.

Pharmacokinetic and statistical analysis

Plasma concentration–time data were fitted to a bi- or triexponential equation (table I):

$$C = \sum_{i=1}^{n} C_i e^{-\lambda_i t}$$

Initial estimates of the parameters C_i and λ_i were obtained with the method of residuals [3]. Final estimates were calculated by the non-linear least-squares regression program of SAS [4] with the Marquardt algorithm and weighting by the inverse square of the plasma concentration. The goodness of fit was judged by the F ratio test [5], standard deviations on parameters and scatter diagrams of the residuals between measured and predicted plasma concentrations. Plasma clearance (Cl), volumes of distribution (Vd^{ss}, Vd^{area}), half-lives ($T_{\frac{1}{2}}$) and mean residence times (MRT) were calculated by standard methods [3].

Analysis of variance [4] was applied to Vd^{ss}, Vd^{area}, Cl, MRT and $T_{\frac{1}{2}}$ to test for differences in these parameters over the studied dose range and effects of anaesthetics. The least significant difference test was used to compare pairs of means. All tests were two-tailed. Statistical significance was declared at $P \leqslant 0.05$. Linear regression was performed to determine if there was any relationship between the pharmacokinetic parameters of droperidol and the factors age and body weight. All results are expressed as mean (SD).

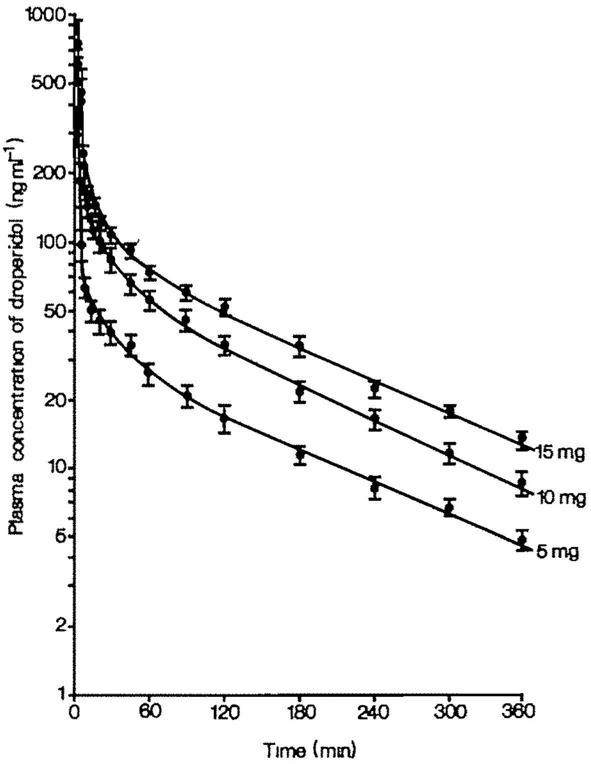

FIG. 1. Mean (SEM) droperidol plasma concentrations after i.v. administration of 5, 10 and 15 mg to surgical patients under neuroleptanalgesia. Expressions describing the time courses of the mean droperidol plasma concentrations were:

$c = 697e^{-0.54t} + 41.5e^{-0.028t} + 26.5e^{-0.0047t}$ (5 mg);

$c = 661e^{-0.30t} + 73.1e^{-0.025t} + 56.2e^{-0.0053t}$ (10 mg);

$c = 853e^{-0.38t} + 83.2e^{-0.031t} + 87.0e^{-0.0053t}$ (15 mg).

RESULTS

After i.v. administration of droperidol its plasma concentrations decreased rapidly during the first 15 min (fig. 1). Following the distribution phase, concentrations decreased in parallel for the three doses. Plasma concentration–time profiles in some individuals were best characterized by a biexponential equation, whereas a triexponential model fitted the data more closely in others. The model-independent kinetic parameters in the neuroleptanalgesia groups are shown in table II. There

TABLE II. *Model-independent pharmacokinetic parameters of droperidol 5, 10 and 15 mg i.v. under neuroleptanalgesia*

Patient	Sex	Age (yr)	Weight (kg)	Vd^{ss} (litre)	Vd^{area} (litre)	Cl (ml min^{-1})	MRT (min)	$T_{\frac{1}{2}}$ (min)
Droperidol 5 mg								
1	M	28	70	94	108	932	101	81
2	F	59	62	73	88	595	122	102
3	F	54	70	38	71	483	79	102
4	F	57	70	169	177	883	191	139
5	F	61	57	135	174	923	146	131
6	M	62	68	216	277	664	325	289
7	F	53	58	67	70	469	142	103
8	F	44	68	81	112	595	136	131
9	M	37	55	80	99	616	129	112
10	F	43	70	103	118	636	162	128
Mean		50	65	106	129	680	153	132
SD		11	6	53	64	173	68	58
Droperidol 10 mg								
11	M	38	70	117	191	688	171	193
12	M	61	90	108	146	717	150	141
13	M	46	78	23	56	400	58	98
14	F	57	83	82	111	455	181	169
15	F	23	48	38	53	426	89	87
16	F	56	86	89	111	713	125	108
17	F	34	74	65	74	580	112	89
18	F	31	52	245	285	1738	141	114
19	F	22	74	87	94	670	129	98
20	F	60	77	124	156	624	198	173
Mean		43	73	98	128	701	135	127
SD		15	14	61	71	384	43	39
Droperidol 15 mg								
21	F	36	70	87	101	676	129	103
22	M	44	80	113	135	674	168	139
23	F	54	70	84	137	725	116	131
24	F	53	55	72	94	517	139	126
25	F	17	60	91	103	741	122	96
26	M	34	69	96	101	721	133	98
27	M	57	67	101	124	706	143	122
28	M	72	48	129	134	873	148	107
29	F	14	58	94	99	674	139	102
30	F	65	75	182	197	1833	99	75
Mean		45	65	105	123	814	134	110
SD		19	10	31	31	368	19	19

were no significant differences between the pharmacokinetic parameters at the different doses. Combination of the 5-, 10- and 15-mg data ($n = 30$) produced a pooled mean elimination half-life of 127 ± 37 min, a plasma clearance of 798(39) ml min^{-1} and volumes of distribution of 111 (50) litre (Vd^{ss}) and 145 (64) litre (Vd^{area}). Volumes of distribution and clearance values were not dependent on age or body weight, as indicated by the low correlation coefficients ($r^2 < 0.13$).

Concomitant use of volatile anaesthetics did not significantly alter droperidol volumes of distribution and clearance (table III).

DISCUSSION

The present study demonstrated the linearity, or dose-independence, of the kinetics of droperidol after single i.v. administration of 5, 10 and 15 mg—three droperidol doses in the therapeutic range. The similarity of the mean droperidol plasma concentration–time curves at each of the doses suggests that the kinetics do not change as the dose increases. The insignificant differences in volumes of distribution and clearance confirm this independence of dose. Furthermore, the half-life did not change as a function of dose. The kinetic

TABLE III. *Model-independent pharmacokinetic parameters of droperidol 10 mg under volatile anaesthesia*

Patient	Sex	Age (yr)	Weight (kg)	Vd^{ss} (litre)	Vd^{area} (litre)	Cl (ml min^{-1})	MRT (min)	$T_{\frac{1}{2}}$ (min)
Halothane								
31	M	15	100	64	114	503	127	158
32	M	52	73	138	215	1076	128	139
33	M	35	68	134	198	1008	133	136
34	M	29	73	233	285	1198	194	165
35	M	26	85	155	252	1008	154	173
36	M	42	65	72	126	705	102	124
Mean		33	77	133	198	916	140	149
SD		13	13	62	68	260	31	19
Enflurane								
37	M	21	75	97	115	828	117	96
38	M	24	85	105	123	934	112	91
39	M	61	70	147	207	1075	137	133
40	F	36	60	135	182	1181	114	107
41	M	36	73	158	222	957	165	161
42	F	47	60	151	238	1096	138	151
Mean		38	71	132	181	1012	131	123
SD		15	10	25	52	128	20	29

parameters obtained in this study were very similar to those previously reported by Fischler and colleagues [2]. In contrast to the present study, they determined the kinetics of droperidol at only one dose—150 μg kg^{-1}, corresponding to a 10-mg total dose.

The volatile anaesthetics halothane and enflurane did not significantly affect the kinetics of droperidol, probably because interindividual variability existed under each condition of anaesthesia. The clearance of droperidol 10 mg ranged from 400 to 1738 ml min^{-1} in neuroleptanalgesia, from 503 to 1198 ml min^{-1} in the halothane group and from 828 to 1181 ml min^{-1} in the enflurane group. Thus the ranges of clearances do not appear to differ. The same considerations are relevant to the volumes of distribution and half-lives.

Normalizing the clearance and volumes of distribution for body weight did not decrease the interindividual variability. Coefficients of variation on weight-normalized parameters were as large as for the uncorrected parameters. Clearance and volumes of distribution were also not influenced by age, at least in the range 14–65 yr.

In conclusion, droperidol i.v. in three therapeutic doses exhibited dose-linear kinetics under neuroleptanalgesia, and the kinetics were not greatly influenced by volatile anaesthetics. Further, the present study indicated that age and body weight of the normal population of adult surgical patients had no clinically relevant influence on the kinetics of droperidol.

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A PHARMACOKINETIC STUDY OF MIDAZOLAM IN PAEDIATRIC PATIENTS UNDERGOING CARDIAC SURGERY

H. M. L. MATHEWS, I. W. CARSON, S. M. LYONS, I. A. ORR, P. S. COLLIER, P. J. HOWARD AND J. W. DUNDEE

SUMMARY

Midazolam 0.3 mg kg^{-1} was given as a single dose to three groups of children undergoing cardiac surgery to determine its pharmacokinetic profile in this situation. The first group, undergoing closed heart surgery, received the midazolam during the operation. The other groups underwent cardiopulmonary bypass (CPB) with and without complete circulatory arrest. Mean clearance was 512 ml kg^{-1} h^{-1} and mean elimintion half-lives were 3.3 h following CPB, with a tendency to a higher clearance in those children who had not undergone bypass. In a subsequent part of the study, 10 children received an infusion of midazolam 0.05 mg kg^{-1} h^{-1}, in combination with intermittent doses of morphine, in the postoperative period. Mean plasma midazolam concentrations consistent with adequate sedation were 80–100 ng ml^{-1} during the infusion. One child who had not undergone CPB had very low plasma concentrations of midazolam with the same rate of infusion, consistent with the tendency for higher clearance in this group in the bolus pharmacokinetic study.

Midazolam, a water-soluble benzodiazepine with a minimal depressant effect on the cardiovascular system [1], is used as a sedative during and after operation in children undergoing open and closed heart surgery. However, little is known of its pharmacokinetic profile in this situation. This study was carried out to determine the pharmacokinetics of a single bolus dose of midazolam given i.v. to patients in this age group, and to ascertain what effect the low temperature and circulatory arrest might have on the subsequent ability of the liver to metabolize midazolam. In a subsequent study, children received an infusion of midazolam in the postoperative period and plasma concentrations were measured and pharmacokinetic variables calculated.

PATIENTS AND METHOD

Consent for the study was obtained from the University Medical Ethics Research Committee.

Infants, older than 3 months, and young children weighing 5–25 kg were studied; none had been prescribed benzodiazepines in the previous 2 weeks and none had any evidence of liver dysfunction. Premedication was with Toronto Catheter Mixture CM3 (chlorpromazine 6.25 mg, promethazine 6.25 mg and pethidine 25 mg per millilitre) 0.1 ml kg^{-1} in children weighing up to 10 kg or with trimeprazine 2 mg kg^{-1} in children weighing more than 10 kg. All received midazolam 0.3 mg kg^{-1} given via a central vein.

Three groups were studied in the bolus dose pharmacokinetic study. The first (A) was undergoing closed heart surgery without cardiopulmonary bypass (CPB) and received midazolam during surgery. The others received midazolam after the operation; 50% of these (B) had undergone CPB and the others (C) had undergone

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TABLE I. *Indications for surgery in the single bolus pharmacokinetic study. A = Closed operations; B = cardiopulmonary bypass, no arrest; C = CPB, circulatory arrest*

A	B	C
5 Coarctation of aorta	3 Fallot's tetralogy	3 Transposition of great vessels
1 Tricuspid valve shunt	1 Atrial septum defect	1 AV canal
	1 Mitral valve stenosis	1 Mitral stenosis
	1 Pulmonary valve infundibular stenosis	

CPB with a period of complete circulatory arrest.

Anaesthesia was induced in all groups with air–oxygen and halothane, muscle paralysis was provided with pancuronium 0.1 mg kg^{-1} and, after intubation of the trachea, anaesthesia was maintained with air–oxygen and halothane in combination with fentanyl 10 µg kg^{-1}, if required. Group A patients received midazolam during the operation once anaesthesia was stable and an arterial cannula had been inserted.

Arterial blood samples (1 ml) were taken from the arterial cannula before the administration of midazolam and at 5, 10, 15, 30, 45, 60 and 90 min and 2, 4, 6, 8, 10, 12 and 24 h after administration. Samples were centrifuged within 24 h, the plasma stored at −20 °C and subsequently analysed for total plasma midazolam concentration using gas–liquid chromatography. The coefficient of variation of the method was 2–4% over the range of concentrations obtained in this study [2]. Elimination half-life, clearance and volumes of distribution were calculated using standard non-compartmental methods [3,4]. Distribution half-life was obtained from a bi-exponential fit to the plasma data using a non-linear least squares regression analysis program [5].

In the second part of the study, 10 children received an infusion of midazolam for sedation in the period following cardiac surgery: nine had undergone cardiopulmonary bypass. No benzodiazepines were administered before or during the operation. In the postoperative recovery ward the children received a bolus dose of midazolam 0.05 mg kg^{-1} followed immediately by an infusion of midazolam 0.05 mg kg^{-1} h^{-1} (via a central vein). Morphine 0.2–0.5 mg was prescribed, as required. Samples of arterial blood (1 ml) were taken before the administration of midazolam and at 7.5, 15, 30, 60 and 90 min, and 2, 4, 6, 8, 10 and 12 h during the infusion. A further sample was taken before the discontinuation of the infusion at 06.00 h on the following morning and at 2, 4, 6, 12 and 24 h following discontinuation. Total plasma midazolam concentrations were estimated as previously described.

Where applicable, the findings are expressed as mean (SD) and differences between means calculated by Student's *t* test.

Children were considered to be adequately sedated when they tolerated synchronized intermittent mandatory ventilation without the use of myoneural blocking drugs. They were not expected to be deeply asleep, but were easily rousable and responding to tracheal suction. Intermittent morphine was prescribed as required, as is the usual practice in our unit.

RESULTS

The indications for operation in the patients in the single bolus pharmacokinetic study are shown in table I. The children who had undergone complete circulatory arrest were significantly younger and weighed significantly less than those in the other groups (table II). Figure 1 shows the mean plasma concentrations obtained in all groups over a 12-h period.

Pharmacokinetic data in table III show that $T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$ and the clearance of midazolam were remarkably similar in groups B and C. Children who had not undergone cardiopulmonary bypass (A) tended to have a higher clearance of midazolam than the other groups but, because of the large variability in readings, the difference was not significant. Volumes of distribution were similar in all groups.

TABLE II. *Patient data (mean (SD)). Single bolus dose study*

Group	Age (yr)	Weight (kg)
A	5.2 (2.53)	18.4 (8.73)
B	4.7 (2.60)	15.9 (6.40)
C	1.3 (0.42)	8.8 (1.29)

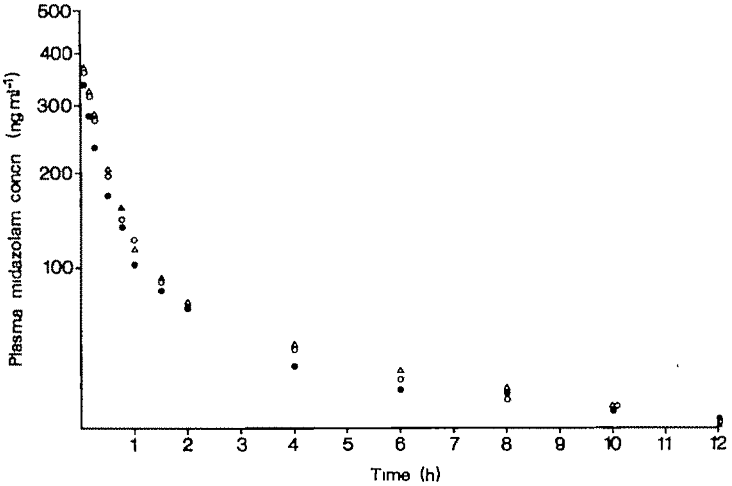

FIG. 1. Mean plasma midazolam concentrations following a single injection of 0.3 mg kg^{-1} i.v. △ = CPB+circulatory arrest; ○ = CPB; ● = closed heart surgery.

TABLE III. *Pharmacokinetic data (mean (SD)). Bolus dose study*

Group	$T_{\frac{1}{2}}^{\alpha}$ (h)	$T_{\frac{1}{2}}^{\beta}$ (h)	Clearance (ml kg^{-1} h^{-1})	V^{ss} (litre kg^{-1})	V^{area} (litre kg^{-1})
A	0.4 (0.21)	2.8 (0.89)	719 (400.6)	1.89 (0.243)	2.47 (0.686)
B	0.3 (0.16)	3.3 (0.53)	512 (108.9)	1.85 (0.283)	2.43 (0.447)
C	0.3 (0.08)	3.3 (0.83)	544 (201.1)	2.02 (0.858)	2.72 (1.429)

The indications for operation and the anthropomorphic data of the children who received an infusion of midazolam are shown in table IV. The child (No. 10) who underwent repair of coarctation of aorta without cardiopulmonary bypass is excluded from these calculations and is discussed separately, as his plasma concentrations were much lower than those of the other nine patients who had undergone cardiopulmonary bypass. The mean duration of the infusion was 16 (1.5) h.

TABLE IV. *Physical characteristics and lesions requiring surgery in infusion group. VSD = Ventricular septum defect*

Patient No.	Age (yr)	Sex	Weight (kg)	Defect requiring surgery
1	8	F	20	VSD and mitral valve
2	4	M	14	VSD
3	2	M	11	AV canal defect
4	6	F	16	Fallot's tetralogy
5	2	F	12	ASD
6	8	M	17	Fallot's tetralogy
7	4	F	14	VSD
8	3	M	12	Fallot's tetralogy
9	5	M	17	VSD
10	7	M	25	Coarctation of aorta

Figure 2 shows the mean plasma concentrations of the nine patients and compares these with those of child No. 10 (no CPB). Mean plasma concentrations of 80–100 ng ml^{-1} were rapidly attained and maintained during the period of study. However, in this one child the plasma concentrations were very low although he received the same rate of infusion of midazolam; this was reflected by very inadequate sedation during the study period. Eight of the other nine patients were adequately sedated and required an average dose of morphine 8.2 mg (range 2.5–15 mg) during the period of the infusion. However, one 20-kg baby with Down's Syndrome (No. 1) was inadequately sedated and required morphine 43.5 mg over 17 h. The plasma concentrations in this patient ranged between 50 and 70 ng ml^{-1}.

Individual clearances calculated from infusion rate divided by the steady state concentration averaged 575 (SD 208.3) ml kg^{-1} h^{-1}. V^{area}, calculated from $(Cl \times T_{\frac{1}{2}}^{\beta})/0.693$, averaged 2.3 (1.06) litre kg^{-1}. The clearances and the V^{area} in the infusion study were not significantly different from those values obtained from the single bolus pharmacokinetic study.

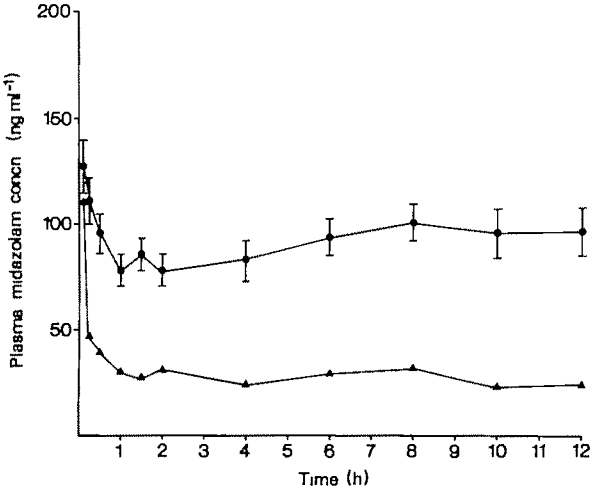

FIG. 2. Mean (SEM) plasma midazolam concentrations during infusion in nine patients (●) and in one patient who had undergone repair of coarctation of aorta (▲).

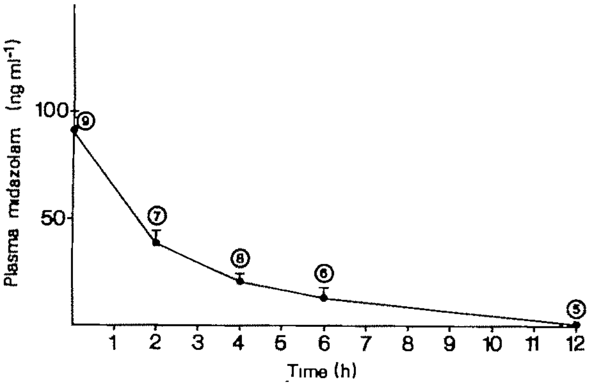

FIG. 3. Mean (SEM) plasma midazolam concentrations following discontinuation of infusion. Actual number of blood samples shown in circles.

Figure 3 shows mean plasma concentrations following discontinuation of the infusion, with values decreasing to less than 40 ng ml^{-1} within 2 h of discontinuation. No midazolam was detected in any of the 24-h samples. The mean elimination half-life, calculated from individual decay curves, was 3.1 (1.36) h. The elimination half-life could not be calculated in the patient who had not undergone CPB, as no midazolam could be detected 2 h following discontinuation of the infusion. Tracheal tubes were removed in a mean of 154 (38.0) min following discontinuation.

DISCUSSION

In an earlier study on the pharmacokinetics of midazolam in normal children [6] the elimination half-life was found to be shorter (1.42 h (0.49)) than in the present investigation. In that study, clearance increased as the dose of midazolam was increased, but the clearance when midazolam 0.3 mg kg^{-1} was given was similar to the clearance obtained in the present study following cardiopulmonary bypass. Volume of distribution was less than in our study, accounting for the decreased elimination half-life. However, when one compares the findings in those children who had undergone CPB with children who had not, there is a tendency for clearance of midazolam to be lower following bypass. The procedure causes hypotension with altered regional blood flow, changes in plasma protein binding as a result of haemodilution and heparinization and hypothermia which may diminish metabolic clearance [7].

In the period after bypass Koska, Romagnoli and Kramen [8] reported a prolongation of the terminal elimination half-life of fentanyl, correlating with a 30 % decrease in hepatic perfusion. Metabolism of midazolam has been shown to be slower in the post-bypass period [9], but no prolongation of lorazepam elimination half-life has been demonstrated [10]. The metabolic pathway of lorazepam primarily involves glucuronide conjugation, liver disease having little effect on this process. Midazolam, on the other hand, is metabolized by hepatic mixed function oxidation followed by glucuronidation. These differences in metabolism may account for the different effects of bypass on the kinetics of lorazepam and midazolam.

Harper and his colleagues [11] studied the pharmacokinetics of midazolam in seven adults following CPB; the mean clearance was 374 ml kg^{-1} h^{-1} with a mean elimination half-life of 4.0 h. The latter is slightly prolonged for adults, but this was considered to be the result of an increased volume of distribution, rather than a decreased clearance in the period after bypass. The clearance found in our children was higher than in the adults and this could be explained by the increased liver blood flow per kg body weight. The hepatic extraction ratio of midazolam varies from 0.3 to 0.7, the liver clearing one- to two-thirds of the blood passing through it. Therefore the metabolism of midazolam depends on the intrinsic hepatic clearance and the hepatic blood flow [12]. The tendency for decreased hepatic clearance of midazolam following CPB in these children may result from a decrease in hepatic perfusion with a decreased metabolic activity of the liver enzymes caused by hypothermia.

Having determined from the single bolus study that there are no pharmacokinetic reasons why midazolam should not be used for sedation following cardiac surgery, infusions of midazolam were used to provide sedation in the postoperative period in children, since a previous study in adults had shown that infusions produce more stable plasma concentrations than do intermittent injections following cardiopulmonary bypass [13]. Midazolam starts to be effective at plasma concentrations greater than 40 ng ml^{-1}, with a good sedative effect between 80 and 100 ng ml^{-1}; values greater than 100 ng ml^{-1} produce sleep in certain adult subjects [14]. In this study mean concentrations of 80–100 ng ml^{-1} were rapidly achieved with a bolus dose of 0.05 mg kg^{-1} followed by an infusion at 0.05 mg kg^{-1} h^{-1}. With this regimen and additional morphine as required, eight of the 10 patients were considered by the nursing staff to be adequately sedated.

Lloyd-Thomas and Booker [15] gave midazolam by infusion to 10 children during and following cardiopulmonary bypass, but found that plasma concentrations greater than 250 ng ml^{-1} were required for adequate sedation. Their patients were asleep, tolerating artificial ventilation and able to respond slightly to nursing procedures such as tracheal suction. These patients received a bolus dose of midazolam 0.2 mg kg^{-1} followed by an infusion at a mean rate of 0.17 mg kg^{-1} h^{-1} in combination with an infusion of morphine 0.02 mg kg^{-1} h^{-1} and vecuronium 0.04 mg kg^{-1} h^{-1}, if required. Thus the dose of midazolam given to these patients was about three times that given to our patients, and this could explain the differences in plasma concentrations in the two studies.

Only two patients in our infusion study were considered to be inadequately sedated and yet the actual concentrations of midazolam in the other eight patients (40–150 ng ml^{-1}) were much lower than in the study by Lloyd-Thomas and Booker. The child who had undergone CPB and was particularly restless was a baby with Down's Syndrome, and these children can be difficult to sedate. Our patients received morphine intermittently without a myoneural blocking agent and the mean requirements were greater than in the other study. Perhaps the level of sedation required in our unit was less than that of the Liverpool group, otherwise it is difficult to explain the disparity in concentrations required to produce adequate sedation.

The patient who underwent repair of coarctation of aorta without bypass had very low plasma concentrations and was inadequately sedated. We can offer no explanation for this anomaly, except the possibility of higher clearance found in the patients not subjected to CPB in the single bolus pharmacokinetic studies. If sedation is required in children who have not undergone CPB, higher rates of infusion may be needed. The values for clearance and elimination half-lives in the other nine patients agree with those found in the single bolus pharmacokinetic studies. In this study, the clearance was greater and $T_{\frac{1}{2}}^{\beta}$ of shorter duration than was our experience with adults who had infusions of midazolam following cardiopulmonary bypass [13].

There are no pharmacokinetic reasons why midazolam should not be given to children both during and after cardiac surgery. The infusion of midazolam in combination with intermittent morphine provided adequate sedation in most of our children.

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TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN THE MANAGEMENT OF ACUTE POSTOPERATIVE PAIN

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SUMMARY

Twenty patients undergoing decompressive lumbar laminectomy were randomly allocated, in a double-blind manner, to receive active or inactive transcutaneous electrical nerve stimulation (TENS) as part of the management of their postoperative pain. All patients received the same non-narcotic general anaesthetic. The efficacy of the TENS was assessed by using a patient-controlled analgesia system (PRODAC) which delivered morphine i.v. This system recorded the number of demands for analgesia and the total dose administered in the first 24 h. In addition, plasma morphine concentrations were measured hourly for the first 6 h and again at 24 h. There was no statistical difference between the two groups in the number of patient demands for analgesia, morphine dose or plasma morphine concentration. TENS offered no advantage over a placebo in the management of acute postoperative pain in these patients.

Following the introduction of the gate control theory of pain by Melzack and Wall [1], Transcutaneous Electrical Nerve Stimulation (TENS) has established an important and effective role in the management of chronic pain [2, 3].

Its use in the management of acute postoperative pain was reported first by Hymes and colleagues [4] and is of less well documented efficacy owing to the lack of well controlled studies.

As an adjunct to postoperative pain relief, TENS is said to have the advantage of being non-toxic, non-invasive, continuous and simple to use [5]. In comparison with opioids, TENS avoids the problems of respiratory depression, sedation and nausea. In contrast to extradural analgesia, TENS does not require high dependency nursing and is not associated with orthostatic hypotension or urinary retention. Studies have reported, in addition to improved pain relief [6–8], a reduced incidence of postoperative ileus [9] and fewer pulmonary complications [10].

Despite the numerous investigations of TENS in the postoperative period, none appears to fulfil the criteria for a randomized prospective double-blind placebo-controlled study nor to include a control group of patients undergoing the same anaesthetic and the same operation. This study was designed to assess the efficacy of TENS when used in the acute postoperative period. Two patient populations receiving the same anaesthetic for identical surgical procedures were compared: one provided a control "placebo" group receiving no electrical stimulation—from inactive TENS machines.

The efficacy of TENS was assessed using morphine demand analgesia (PRODAC) by comparing: the number of patient demands for analgesia; the total dose of morphine delivered by a demand machine; and the plasma concentration of morphine attained.

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PATIENTS AND METHODS

Local ethics committee approval was obtained for this study. Twenty patients (table I) undergoing decompressive lumbar laminectomy were studied.

All patients were seen at a preoperative visit when they were invited to participate in the study and consent was obtained. They were randomly assigned in a double-blind manner, to one of two groups: group A ($n = 10$) to receive an inactive TENS device to use during the acute postoperative period (first 24 h) and group B ($n = 10$) to receive an active device.

Instructions were given by the anaesthetist on the use of the TENS and demand analgesia equipment. No explanation was given of the sensation to be experienced when using TENS, simply the instruction that, on regaining consciousness and feeling pain the patient should adjust the pulse amplitude control of the stimulator until they felt comfortable. If this proved insufficient, additional analgesia could then be obtained by pressing the button of the demand analgesia machine. All patients were offered continued use of the TENS for postoperative analgesia after the 24-h study period.

Anaesthetic technique

Both groups received the same narcotic-free anaesthetic. Following premedication with lorazepam by mouth, anaesthesia was induced with thiopentone and the trachea intubated when neuromuscular blockade had been achieved using alcuronium. Anaesthesia was maintained by ventilation of the lungs with halothane vaporized in 70% nitrous oxide and oxygen until the end of surgery when halothane and nitrous oxide were discontinued and neuromuscular blockade was antagonized. The patient was then transferred (still asleep) to the recovery ward; on regaining consciousness he was transferred to a high dependency unit for the 24 h of the study.

TABLE I. *Characteristics of patients (mean ± SD) and analgesic requirement in the presence of active and inactive TENS. No significant difference between groups (Mann–Whitney* U *test)*

	Group A (inactive)	Group B (active)
Number	10	10
Male: Female	5:5	2:8
Weight (kg)	70.3 ± 11.6	67.7 ± 10.0
Age (yr)	44.6 ± 9.1	45.7 ± 11.7
Total No. demands	114.9 ± 79.5	107.6 ± 64.7
Total morphine dose (mg)	55.4 ± 3.6	54.0 ± 3.2

Demand analgesia

PRODAC (Department of Engineering Science, University of Oxford) is a fully programmable device for patient-controlled drug delivery and has been described previously [11]. It consists of three separate units: a dedicated programmable microcomputer, a small syringe driver (MS16 Graseby Dynamics) and a push-button held by the patient. Fixed volumetric boluses are delivered in response to each button press and safety limits are applied to the total volume that can be delivered in any 1 min. Morphine was the drug chosen for this study, delivered in boluses of 0.05 mg. The microcomputer times and records all demands made by each patient. This computer record and the plasma morphine concentrations achieved were analysed to assess the degree of pain relief associated with use of TENS.

Transcutaneous Electrical Nerve Stimulation

All patients were familiar with the TENS device (Wright Care Dual Channel System, Dow Corning Wright, Arlington, Tennessee), having had a "practice" model in their possession for at least 12 h before surgery. At the end of surgery two sterile 15-cm electrodes were placed longitudinally beside the incision and a further two were trimmed and placed at either end at 90° (fig. 1). All patients were observed by an anaesthetist in the recovery area to ensure they switched on and made use of TENS, after regaining consciousness. The patient was then encouraged to adjust the TENS amplitude. At the end of the study period (after 24 h) all patients were given the option of retaining or discontinuing use of their stimulators.

The stimulator current properties of the

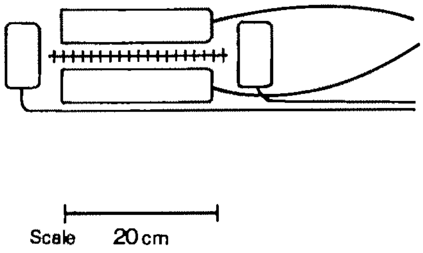

FIG. 1. Schematic placement of dual channel TENS electrodes around laminectomy incision.

Wright Care System broadly conform with those suggested by Tyler and colleagues [5] as being the most effective for treating acute postoperative pain. In this study TENS consisted of an asymetric biphasic waveform of 180 μs pulse width and a fixed frequency of 70 Hz. Placement of TENS electrodes as shown in figure 1 has been described and recommended in previous studies using TENS in the presence of spinal and other surgical incisions [12].

Blood sampling

Blood was withdrawn and plasma morphine concentrations measured by a radioimmunoassay technique [13] immediately before the commencement of demand analgesia, and at 1-h intervals for 6 h and again at 24 h.

Statistical analysis

Non-parametric statistical analysis of the results was performed using the Mann–Whitney *U* test for comparison of groups. A probability value of less than 0.05 was considered to be significant.

RESULTS

No complicatons or difficulties were encountered in either group as a direct result of the use of the TENS system. All patients were sufficiently familiar with the stimulator box and its controls to be able to begin using TENS shortly after regaining consciousness. Although personal assessment of postoperative analgesia was not recorded as a part of this study it was noted that, whilst demand analgesia found almost universal patient approval, only two patients, both from group B (active TENS), considered TENS worth continuing beyond the initial 24-h study period.

The need of patients in both groups to make use of demand analgesia is recorded in figure 2 and shows that TENS did not significantly alter the rate of demand. There was an apparently increased demand rate in group B during the 3rd hour after operation which was accounted for by one particular patient who made 47 demands within 1 h and, thereafter, made virtually no further use of demand analgesia. This unusually high demand rate resulted in the highest recorded plasma morphine concentration (1617 nmol litre^{-1}).

The similar requirement for morphine analgesia in the two groups was reflected by plasma morphine concentrations which were not significantly different (fig. 3) during the first 24-h in the postoperative period.

DISCUSSION

In this study TENS was no better than a placebo in producing relief of acute postoperative pain in a double-blind, placebo-controlled study of patients who had the same anaesthetic and operation.

This conclusion is based on the finding that irrespective of the activity of the TENS stimulator, there was no significant difference in either the number of demands for analgesia or the total dose of morphine delivered (table I). The pattern of demand by both groups for analgesia was

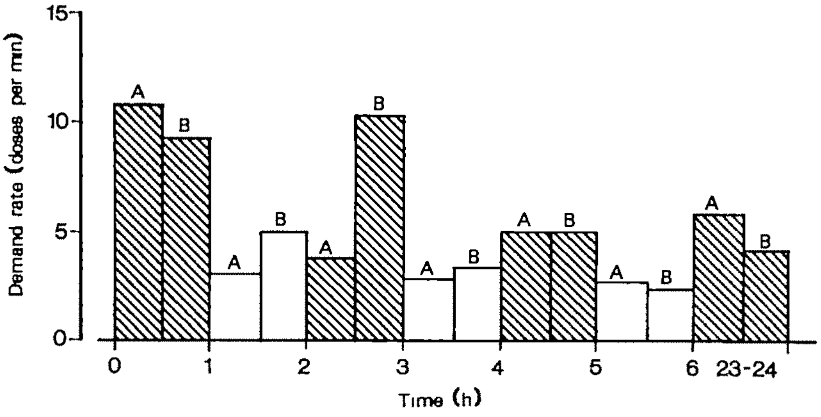

FIG. 2. Mean bolus demand rate during patient-controlled demand analgesia in patients following decompressive lumbar laminectomy, receiving inactive (group A) or active (group B) transcutaneous electrical nerve stimulation.

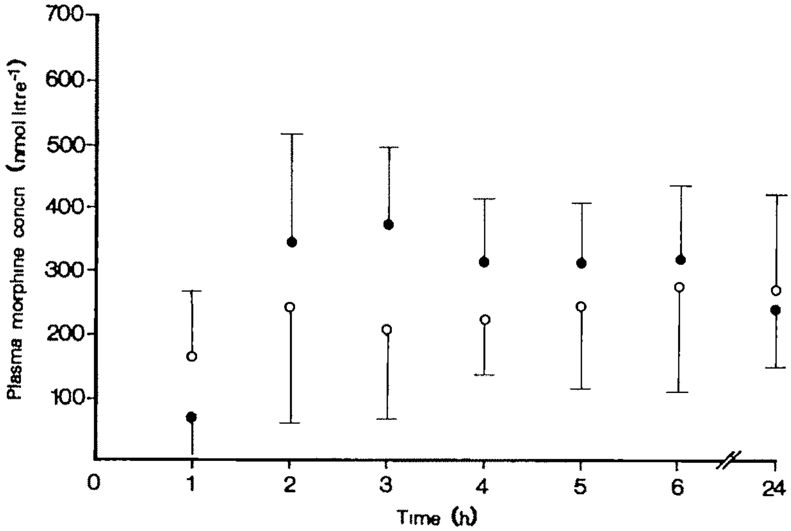

FIG. 3. Mean (±SEM) plasma morphine concentrations during demand analgesia following decompressive laminectomy in patients receiving inactive (○, group A) and active (●, group B) transcutaneous electrical nerve stimulation.

similar. In addition, the resultant plasma morphine concentrations were similar in both groups. This suggests that the pain experienced and the analgesia requirement were similar in both groups and that, therefore, the active group was uninfluenced by the TENS.

In contrast to the majority of the previous studies of the postoperative use of TENS, we designed this study as a double-blind placebo-controlled study with comparisons made between similar groups of patients undergoing the same operation and anaesthetic technique.

Compared with previous TENS studies, this investigation differed in that it used demand analgesia as a means of assessing the effect of TENS on postoperative pain. Demand analgesia and the degree to which it is used to supplement other pain relief techniques has been suggested as a measure of the effectiveness of the accompanying technique [14].

Patients were not informed what sensations they were likely to experience from TENS, as this was considered to invalidate the blinding of a placebo-controlled study. However, instruction in the use of TENS and the opportunity to operate practice equipment was probably far greater than that offered to patients in the pain clinic, where TENS has proved to be of benefit. A difference in analgesic requirement could, therefore, still be expected if TENS improved the management of acute postoperative pain in the first 24 h.

Demand analgesia may itself have concealed any beneficial effects of TENS. However, the converse is also possible: if TENS was as good as demand i.v. morphine, the gold standard, then the study would have shown this. Demand analgesia was uniformly well received by all patients and, despite preoperative advice to adjust and use TENS as an initial part of pain relief, it is possible that the immediate and satisfactory analgesia available on demand may have discouraged patients from persevering fully with the use of TENS. To answer this point, it would be necessary to know if the patient made a serious attempt to use the TENS machine for pain relief before turning to demand analgesia. Unfortunately, the design of this study did not permit evaluation and comparison of TENS usage.

In spite of randomized patient selection, there does appear to have been a preponderance of females in group B (active TENS) where the male:female ratio was 1:4. Despite the small sample size, the groups do otherwise appear to be comparable. The overall male:female ratio for all patients undergoing laminectomy in the Radcliffe Infirmary over the period of this study was equal; that is, the same as group A. Keats [15], examining a number of variables in the presence of acute postoperative pain, found no relationship between sex and pain severity. This has been confirmed by a number of subsequent studies [16, 17]. Thus the female preponderance in group B should not compromise the study and this is reinforced by the fact that all of the recorded variables (numbers of demands, total dose of morphine and blood concentrations) were similar in both groups.

The results of this study do not accord with some of the previously published results [4, 7, 8], but do support the findings of Menzel and Martinson [18] who, using staff-administered narcotics as a measure of the efficacy of TENS, similarly found that there was no improvement in postoperative pain relief as a result of active stimulation.

The lack of response to TENS as found in the postoperative period when compared with its successful use in chronic pain may indicate a difference in the pain mechanisms involved. Another possibility is that TENS may be of more use later on in the postoperative period when the pain is less intense or, indeed, after less painful surgery.

ACKNOWLEDGEMENTS

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ORAL NALBUPHINE FOR THE TREATMENT OF PAIN AFTER DENTAL EXTRACTIONS

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SUMMARY

A randomized, double-blind comparison of nalbuphine 30 mg or 60 mg by mouth and dihydrocodeine 30 mg by mouth was conducted in 75 patients with moderate to severe pain after surgery for dental extractions under general anaesthesia. A significant reduction in pain intensity followed each treatment and persisted throughout the 4-h observation period after nalbuphine, but only for 3 h after dihydrocodeine was given. Reduction in pain intensity was significantly greater 2, 3 and 4 h after the use of nalbuphine 60 mg than following dihydrocodeine 30 mg, and the mean total pain intensity difference was greater following nalbuphine 60 mg than following dihydrocodeine. Nalbuphine 60 mg effectively provided complete or good pain relief in more than 50% of the patients and only three patients in this group required additional analgesia during the period of observation, compared with nine patients in each of the other groups. However, the patients who received nalbuphine 30 mg had a significantly higher mean pain intensity before treatment than those in the other groups. The side-effects encountered were those typical of opioid medication; there were no statistically significant differences between the groups.

Nalbuphine is a partial agonist opioid that is approximately equipotent with, and has a similar duration of effect to, morphine 8–10 mg [1]. After i.m. injection it has been shown to be effective in the treatment of moderate to severe pain, and to produce a low incidence of side-effects [2]. It has been shown to have a limited respiratory depressant effect in man [3] and to have clinically unimportant cardiovascular and respiratory effects following doses of up to 200 mg given i.v. over 1 h by patient-controlled on-demand apparatus [4]. Nalbuphine has recently been formulated in tablets (30 mg) for administration by mouth.

Dihydrocodeine is an opioid frequently given by mouth as tablets of 30 mg, for the treatment of moderate to severe pain including pain after dental extraction. It has a duration of effect (4–6 h) similar to that of morphine, and has similar side-effects [5].

The aim of the investigation was to compare the efficacy of dihydrocodeine 30 mg by mouth with that of nalbuphine 30 or 60 mg by mouth for the treatment of moderate pain following dental surgery under general anaesthesia.

PATIENTS AND METHOD

The investigation was approved by the Hospital Ethics Committee. Ninety patients (ASA grade I or II) aged between 18 and 60 yr, requiring general anaesthesia for extraction of teeth and who had given written informed consent to participate in the study, were allocated randomly to one of three groups, to receive dihydrocodeine 30 mg, nalbuphine 30 mg, or nalbuphine 60 mg, for the initial treatment of postoperative pain. Before anaesthesia was induced the patients practised the use of a 10-cm horizontal linear analogue scale (LAS) ("None" to "Worst, unbearable"), for recording the degree of pain.

Anaesthesia was induced in the unpremedicated patients with thiopentone—approximately 4 mg kg^{-1} i.v., followed by suxamethonium (1.5 mg kg^{-1}). The trachea was intubated and anaesthesia maintained using nitrous oxide in oxygen

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with clinically appropriate concentrations of enflurane. No analgesics were administered on the day of surgery, before the postoperative analgesic was given. When the patients requested pain relief after recovery from anaesthesia they were given oral medication randomized according to the number of their entry into the study and rendered double-blind by the use of a double-dummy technique.

Before medication the patients indicated the intensity of their pain (by LAS) and this assessment was repeated 0.5, 1, 2, 3 and 4 h after medication, or until another analgesic was given. At each assessment after medication the assessor recorded an opinion regarding pain relief, grading it as 0, 1 (slight), 2 (moderate) 3 (good) or 4 (complete). Any response to non-specific questions regarding side-effects or discomfort was noted also. The intensity of side-effects was graded as mild, moderate or severe, their duration noted, and any medication required to treat them was recorded.

Alternative analgesic therapy was given immediately on demand to any patient who requested it and these patients were withdrawn from the study.

Statistical analysis

Pain intensity scores (LAS) were treated as parametric data and analysed (including pretreatment scores) by repeated measures analysis of variance (using BMDP2V [6]). LAS values missing because of withdrawals from the study were replaced by values calculated by regressing the missing values on the existing pain intensity scores, and also on the pain relief scores using the BMDPAM algorithm [6]. The degrees of freedom for the error terms in the analysis of variance were reduced by the number of missing values involved in the term. For the missing pain relief gradings resulting from withdrawal from the trial, an extra category (withdrawn) was included, to allow the use of a continuation odds model for regression analysis (GLIM algorithm) [7].

The Fisher–Tukey approach to avoid overstating the statistical significance of *a posteriori* tests was used. Duration of effect was assessed by use of the paired *t*-test to compare the 4-h assessments with pre-treatment values. Between-group comparisons of the predicted peak effect of the analgesics were made by comparing pain relief grades at the 2-h assessment, using the Mann–Whitney *U* test. In the case of patients who had already withdrawn from the study, the final grade that had been assessed was recorded for this time. Other categorical data were assessed using the Chi-squared test.

RESULTS

Fifteen of the 90 patients who entered the study were withdrawn before recording of the effects of the medication could start. Some of these vomited shortly after medication; others requested an injection because of severe pain. Full records were obtained for 75 patients: 27 received dihydrocodeine 30 mg, 24 nalbuphine 30 mg and 24 nalbuphine 60 mg. Demographic data are recorded in table I; the groups were similar in composition.

Pain intensity values are illustrated in figure 1.

All the treatments provided some reduction in pain intensity for 3 h. At the 4-h assessment dihydrocodeine was no longer effective, whereas both doses of nalbuphine were still providing a significant reduction in pain intensity ($P < 0.01$; paired *t* test). The reduction in effectiveness of dihydrocodeine towards the end of the observation period is confirmed by the number of patients requiring additional analgesia. Only three patients who received nalbuphine 60 mg required an additional analgesic compared with nine in the group which received dihydrocodeine—eight of these after 3 h. All but five of the remaining patients in this group showed increasing pain between the 3- and 4-h assessments.

Nine patients who received nalbuphine 30 mg also required additional analgesia, eight before 2 h. However, on those occasions when nalbuphine 30 mg was effective, it worked effectively throughout the observation period. The initial mean pain intensity score for the nalbuphine 30 mg group (61.5) was significantly higher than those of the other groups (53 and 52.4, respectively) ($P <$

TABLE I. *Demographic data (mean ± SEM)*

Group	*n*	Age (yr)	Weight (kg)	Height (cm)	Sex
Dihydrocodeine 30 mg	27	27.5 ±2	65.2 ±1.9	168 ±2.1	10F 17M
Nalbuphine 30 mg	24	27.6 ±2	66.8 ±2.1	173 ±2.2	12F 12M
Nalbuphine 60 mg	24	24 ±1.3	62.6 ±2.4	168 ±3.2	9F 15M

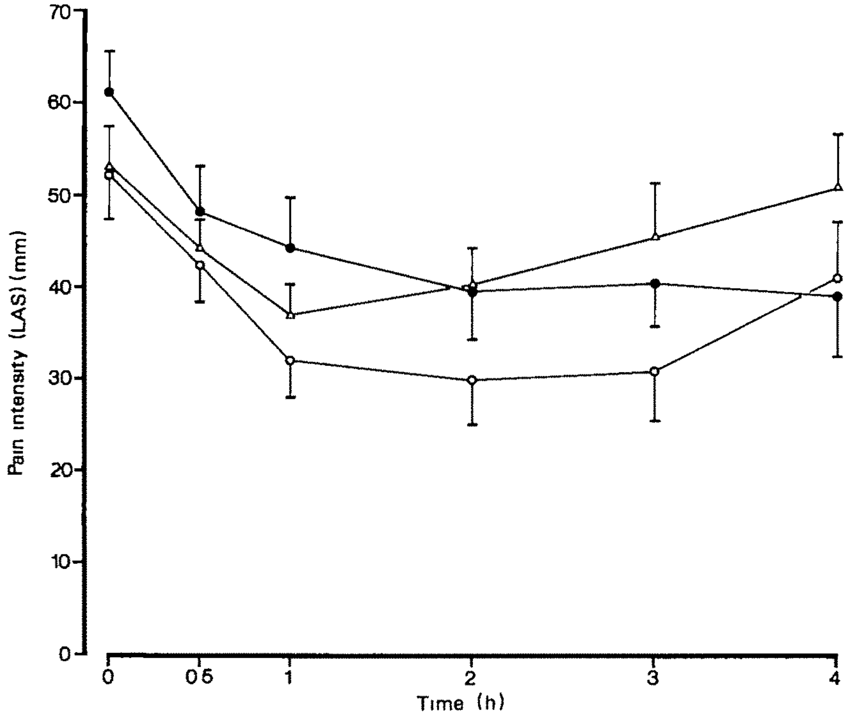

FIG. 1. Mean (SEM) pain intensity scores (linear analogue scale) before (time 0) and after oral medication with dihydrocodeine 30 mg (△, $n = 27$), nalbuphine 30 mg (●, $n = 24$) or nalbuphine 60 mg (○, $n = 24$).

TABLE II. *Mean pain intensity (LAS).* $*P < 0.05$ *analysis of variance (Fisher–Tukey approach)*

Assessment time	Nalbuphine 60 mg	Dihydrococeine 30 mg	Differences between treatments
Before treatment	52.4	53.7	1.3
30 min	40.8	44.7	3.9
1 h	31.2	36.8	5.6
2 h	27.5	40.6	13.1*
3 h	25.8	41.8	16.0*
4 h	34.3	43.7	9.4*
Mean total pain intensity difference ($P = 0.028$)	103.2	56.7	

0.05, *t* test), indicating the recruitment into this group of several patients with more severe pain than the general level observed. Indeed, the patients in the nalbuphine 30 mg group who required additional analgesia had an initial mean pain intensity score of 78.5. It appears to be inappropriate to treat pain of such high intensity with oral medication, and most of these patients required a parenteral opioid.

Because of the difference in pain intensity before medication, and the increased number of early withdrawals compared with the other groups, the nalbuphine 30 mg group was omitted from the between group comparisons of pain intensity and total pain intensity differences. Mean pain intensities (table II) were significantly ($P < 0.05$) lower in the nalbuphine-treated patients than in the dihydrocodeine-treated

TABLE III. *Percentage of patients obtaining complete or good pain relief*

Group	Assessment time (min)					Mean total pain relief score
	30	60	120	180	240	
Nalbuphine 30 mg	21	29	33	29	33	13.1
Nalbuphine 60 mg	25	50	62	50	29	14.7
Dihydrocodeine 30 mg	18	30	22	19	19	12.7

TABLE IV. *Side-effects reported.* n = *Total number of patients in group*

Group	Side-effect	
Nalbuphine 30 mg ($n = 24$)	3 Nausea	(1 severe, 2 mild)
	2 Headache	(moderate)
	1 Drowsiness	(mild)
	2 Light-headed	(mild)
Nalbuphine 60 mg ($n = 24$)	2 Nausea	(moderate, 1 vomited)
	1 Drowsiness	(mild)
	2 Light-headed	(mild)
	1 Itchy nose	(mild)
Dihydrocodeine 30 mg ($n = 27$)	1 { Light-headed Nausea }	(moderate)
	1 Rash	(mild)

patients at 2, 3 and 4 h after medication. The total decrease in pain intensity scores was also greater in the nalbuphine group ($P < 0.05$). The percentage of patients in whom pain relief was assessed as complete or good is indicated in table III, together with the total pain relief scores that were recorded. Only in the nalbuphine 60 mg group did at least 50% of the patients achieve these degrees of pain relief. Two hours after medication, nalbuphine 60 mg provided significantly better pain relief than dihydrocodeine ($P < 0.01$, Mann-Whitney U test).

The number and type of side-effects encountered are listed in table IV and were typically those caused by opioids. There was no statistical difference between the groups. One patient in each of the nalbuphine groups was treated (with an antiemetic) for side-effects before additional analgesics were administered.

DISCUSSION

The comparison made in the present study was primarily that between nalbuphine 60 mg and dihydrocodeine 30 mg and this showed statistical differences between the groups in favour of nalbuphine before withdrawals seriously affected the analysis. Most early withdrawals occurred in the group of patients who received nalbuphine 30 mg, but this observation may be related less to the ineffectiveness of this dose than to the fact that this group contained more patients with severe pain than the other groups, a quirk of random allocation. For these reasons this group was omitted from the analysis of variance used to compare the other groups but, as can be seen in figure 1 (mean pain intensity scores (including substituted values)) and table III (the pain relief obtained), nalbuphine 30 mg was at least as good an analgesic as dihydrocodeine 30 mg and, like the larger dose of nalbuphine, was still effective after 4 h, whereas dihydrocodeine was not.

The statistical assessment of duration of effect was made by comparing pain intensity before treatment with that at the end of the observation period using Student's paired t test. This method of analysis avoids the theoretical problems of assessing probability after multiple testing. For the same reason, between-group comparisons of pain relief were confined to the anticipated time of maximum effect (2 h). From previous experience it was not anticipated that the maximum effect of oral dihydrocodeine after surgery would appear earlier, and this biased this assessment in favour of nalbuphine. In the other analyses the Fisher–Tukey approach was used to maintain at least a minimum statistical significance level when a large number of comparisons are made.

The results of the investigation indicate that nalbuphine by mouth reduces pain after dental surgery. However, whilst a dose of 30 mg is as effective as, and acts for longer than dihydrocodeine 30 mg, nalbuphine 60 mg is significantly more effective than dihydrocodeine, and was the only medication to produce good or complete pain relief in more than 50% of the patients who received it.

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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION WITH NALMEFENE

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SUMMARY

The duration of respiratory depression induced by morphine 10 mg/70 kg was studied following the administration of one of two opioid antagonists. Respiratory measurements included: (i) the ventilatory response to carbon dioxide, described in two ways—the minute ventilation at an end-tidal carbon dioxide partial pressure of 8 kPa ($\dot{V}_{E}8$) and the log slope of the ventilatory response to carbon dioxide; (ii) resting end-tidal carbon dioxide partial pressure; (iii) rate of ventilation. One hour after administration of morphine, one of the following was given i.v.: nalmefene 0.4 mg/70 kg; naloxone 0.4 mg/70 kg (low dose); naloxone 1.6 mg/70 kg (high dose); or saline placebo. The depression of $\dot{V}_{E}8$ by morphine was antagonized by all three treatments for the 1.5 h after the injection. However, for the 1.5–6 h after antagonist, $\dot{V}_{E}8$ following naloxone became depressed, whereas $\dot{V}_{E}8$ after nalmefene remained significantly increased compared with other treatments. Nalmefene restored the slope of the ventilatory response to baseline for 6 h and differed significantly from low but not high dose naloxone. Resting end-tidal carbon dioxide measurements demonstrated that nalmefene activity exceeded that of low but not high dose naloxone over the 1.5–4.5 h period. Rate of ventilation was not different between treatments.

The only pure opioid antagonist available currently for clinical use is naloxone. Its duration of activity is short [1] compared with that of most routinely used opioids [2].

The need for a longer acting antagonist has been highlighted recently by the use of extradural and intrathecal opioids [3]. Unpredictable late ventilatory depression produced by extradural morphine is antagonized selectively by naloxone [4, 5], leaving analgesia intact, but recurs as naloxone activity diminishes. Prolonged opioid antagonism would also be valuable in the intensive care unit when treating opioid overdose or when weaning patients from ventilatory support which has required prolonged opioid sedation.

Nalmefene (17 N-methylcyclopropyl 3-14 dihydroxy 4-5 epoxy morphinan 6 methylene, produced by Schering-Plough Pharmaceuticals) is a new pure opioid antagonist. It is a water soluble naltrexone derivative with pharmacokinetics that suggest a longer duration of action than that of naloxone. The mean terminal β elimination half-life of nalmefene is 8.5 h [6], compared with 1–2.5 h [7, 8] for naloxone. Nalmefene is also more effective than naloxone at inhibiting agonist binding at the central opioid receptor site in the rat [9]. These characteristics and its oral bioavailability are attributed to the exomethylene group found at position 6 of the nalmefene molecule (fig. 1), which blocks one site of metabolism. Nalmefene is metabolized in the liver and excreted in urine as the glucuronide [6]. In clinical studies using healthy volunteers, doses of up to 300 mg by mouth and 24 mg i.v. have been tolerated well, with only mild subjective effects and with no evidence of opioid agonist activity.

We have studied the degree and duration of nalmefene-induced antagonism of respiratory depression produced by i.m. morphine and compared it with high and low doses of naloxone, and a placebo. Both high and equiefficacious doses of

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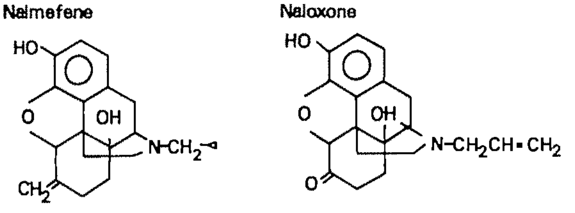

FIG. 1. Molecular structure of nalmefene and naloxone.

naloxone were included in the study, to counter possible criticism that the prolonged duration of activity of nalmefene could be attributed solely to its increased potency.

SUBJECTS AND METHODS

Six healthy male volunteers (ages 29–48 yr, weights 61–90 kg) participated in the study, which was approved by the Harrow District Ethics Committee.

Each subject was studied on four separate days with intervals of at least 1 week. The subjects received morphine 10 mg/70 kg i.m. on each occasion, followed 1 h later by nalmefene 0.4 mg/70 kg, naloxone 1.6 mg/70 kg, naloxone 0.4 mg/70 kg or saline placebo i.v. The test drugs were administered in a double-blind design study in a random sequence. The subjects were allowed light breakfast without tea or coffee, and then fasted throughout the day except for water. Hydration was maintained by an i.v. infusion of 1 litre of 4 % Dextrose and 0.18 % saline solution, which also allowed the test drugs to be administered without the subject's knowledge. All the subjects were studied in the supine position and, except for the experimental procedure, were undisturbed and lay quietly for the whole 8-h period of the study.

Measured variables included resting end-tidal $P\mathrm{CO}_2$, rate of ventilation and the ventilatory response to hypercapnia. The results were obtained during a cycle of testing which lasted approximately 15 min, throughout which the subject wore a noseclip and breathed through a mouthpiece connected to a low resistance circuit. First, with the subject breathing room air via a non-rebreathing valve, the end-tidal carbon dioxide tension ($P\mathrm{E}'_{\mathrm{CO}_2}$) and rate of ventilation were measured over a period of 7 min using a Hewlett-Packard (Model 42710) infra-red analyser. The mean values during each 1-min interval were derived electronically. Subsequently, the ventilatory response to hypercapnia was determined using a modified Read re-breathing method [10, 11]. Subjects breathed 50 % oxygen through a low resistance valve for 3 min before being connected to a rebreathing system primed with a gas mixture containing 6.5 % carbon dioxide and 50 % oxygen in nitrogen. Rebreathing continued until the carbon dioxide concentration increased to 8.5 % or until ventilation increased to 40 litre min^{-1}, whichever occurred first. The gas mixture was contained in an electronic Ohio spirometer which provided an output proportional to volume, and this signal was processed to derive continuous minute ventilation. Minute volume ($\dot{V}\mathrm{E}$) was plotted instantaneously against $P\mathrm{E}'_{\mathrm{CO}_2}$ on a Bryans X-Y recorder.

Three such test sequences were recorded before the administration of i.m. morphine. Testing was recommenced 20 min later and repeated at 20-min intervals for 2.5 h and then every 30 min. Test drugs were injected i.v. 1 h after opioid treatment and subjects were monitored for the subsequent 6 h.

As the reproducibility of respiratory measurements within days is greater than that between days, measurements were assessed relative to baseline values for each study day [12]. Baseline values were obtained from the mean of the last two measurements made before injection of morphine. The values of ventilatory rate and $P\mathrm{E}'_{\mathrm{CO}_2}$ at each time point were obtained from the average of the data obtained over 7 min.

The slopes of the ventilatory response curves were determined by drawing a line of best fit through the linear portion of each curve. These lines were extrapolated to the ventilation at $P\mathrm{E}'_{\mathrm{CO}_2}$ 8 kPa to determine $\dot{V}\mathrm{E}8$. Slope and $\dot{V}\mathrm{E}8$ data were log transformed because the distribution of slopes of ventilatory response to hypercapnia is skewed and log normal [13, 14]. For these two variables, change from baseline was obtained by subtraction after taking logarithms.

Data for the 14 time points following injection of the test drug were analysed by "two-way repeated measures" analysis of variance. To simplify further statistical analysis, data were averaged within three time periods following injection of test drug: the first 1.5 h when the activity of a conventional dose of naloxone would be present and waning, the subsequent 3 h when nalmefene activity is expected to be dominant, and the final 1.5 h to assess possible recurrence of opioid activity.

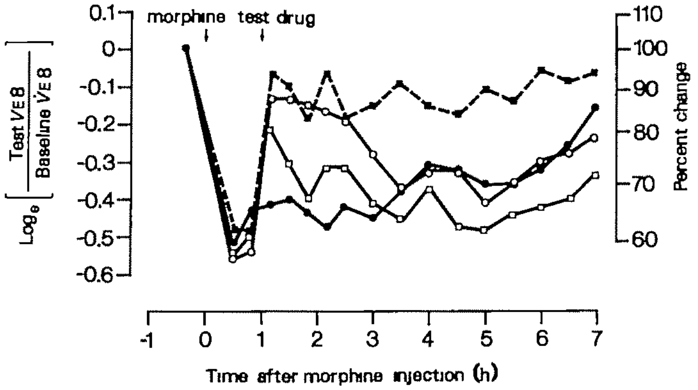

FIG. 2. Time course of changes in minute ventilation at an end-tidal $P\text{CO}_2$ of 8 kPa ($\dot{V}$E8). At zero time morphine was given, and 1 h later one of the three morphine antagonists (■ = nalmefene 0.4 mg/70 kg; ○ = naloxone 1.6 mg/70 kg; □ = naloxone 0.4 mg/70 kg) or saline placebo (●).

TABLE I. *Log* VE8. *Mean values of change from baseline after drug. SEM 1 = SE of each mean in that column; SEM 2 = SE of the difference between any pair of means in the column*

	Time after drug (h)		
Drug	0–1.5	1.5–4.5	4.5–6
Placebo	−0.428	−0.359	−0.246
Naloxone 0.4 mg/70 kg	−0.305	−0.440	−0.396
Naloxone 1.6 mg/70 kg	−0.151	−0.343	−0.264
Nalmefene 0.4 mg/70 kg	−0.119	−0.139	−0.026
SEM 1	0.067	0.062	0.065
SEM 2	0.095	0.088	0.092
P values (*significant)			
Nalmefene *v.* placebo	0.009*	0.03*	0.04*
Nalmefene *v.* naloxone 0.4 mg	0.08	0.006*	0.003*
Nalmefene *v.* naloxone 1.6 mg	0.74	0.04*	0.03*

RESULTS

Two-way analysis of variance, both before and after division into three time periods, showed significant difference between the four treatments for $P\text{E}'_{\text{CO}_2}$, log slope and log $\dot{V}$E8, and demonstrated that the differences varied over time. Rate of ventilation showed no significant difference between any of the drug regimens at any time.

Further analysis comparing the treatments during each time period was undertaken by carrying out paired *t* tests using the residual standard deviations obtained from the analysis of variance. Statistical significance was assigned at $P \leqslant 0.05$.

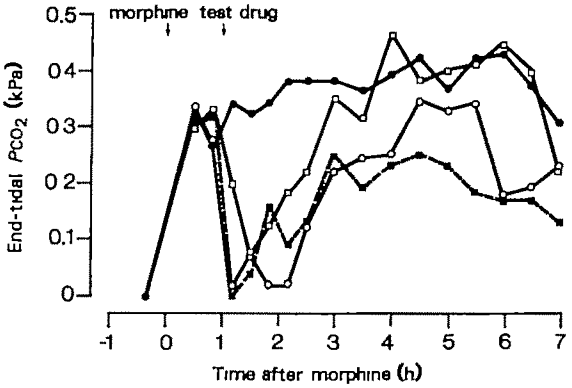

FIG. 3. Changes in end-tidal carbon dioxide partial pressure.

TABLE II. $P_{E'CO_2}$. *Mean values (kPa) of change from baseline after drug*

Drug	Time after drug (h)		
	0–1.5	1.5–4.5	4.5–6
Placebo	0.36	0.40	0.37
Naloxone 0.4 mg/70 kg	0.17	0.39	0.35
Naloxone 1.6 mg/70 kg	0.05	0.30	0.20
Nalmefene 0.4 mg/70 kg	0.09	0.25	0.16
SEM 1	0.08	0.05	0.08
SEM 2	0.11	0.07	0.11
P values (*significant)			
Nalmefene *v.* placebo	0.03*	0.02*	0.07
Nalmefene *v.* naloxone 0.4 mg	0.48	0.03*	0.10
Nalmfene *v.* naloxone 1.6 mg	0.76	0.35	0.70

Log ventilation at end-tidal P_{CO_2} *8 kPa* ($\dot{V}_{E}8$)

Graphical display of averaged data (fig. 2) shows immediate recovery from morphine suppression with nalmefene treatment. Recovery was sustained over the 6-h period studied. Initial recovery with the high and low dose naloxone treatments was followed by a rapid decline and both differed significantly from nalmefene over the final 1.5–6 h period (table I).

Resting end-tidal P_{CO_2}

All three drug treatments were effective initially (fig. 3). Nalmefene was not significantly different from high dose naloxone at any time studied. Low dose naloxone differed significantly from nalmefene only over the middle 3 h (table II). There were no significant differences among any of the treatments, including placebo, after 4.5 h.

Log slope of ventilatory response to hypercapnia

Nalmefene treatment restored the slope of the response curve to baseline values for 6 h (fig. 4). Nalmefene was significantly different from low dose naloxone throughout the period studied (table III).

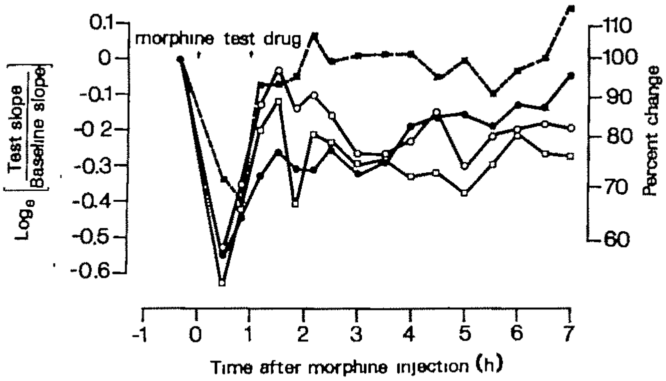

FIG. 4. Changes in slope of ventilatory response to carbon dioxide.

TABLE III. *Log slope. Mean values of change from baseline after drug*

Drug	Time after drug (h)		
	0–1	1.5–4.5	4.5–6
Placebo	−0.292	−0.217	−0.102
Naloxone 0.4 mg/70 kg	−0.255	−0.316	−0.246
Naloxone 1.6 mg/70 kg	−0.119	−0.239	−0.196
Nalmefene 0.4 mg/70 kg	−0.028	−0.024	0.036
SEM 1	0.065	0.087	0.077
SEM 2	0.092	0.123	0.108
P values (*significant)			
Nalmefene *v.* placebo	0.02*	0.15	0.23
Nalmefene *v.* naloxone 0.4 mg	0.03*	0.04*	0.03*
Nalmefene *v.* naloxone 1.6 mg	0.35	0.11	0.06

Side-effects

Three of the subjects complained of paraesthesiae in the mid-thoracic region following the administration of nalmefene. One had a similar complaint following high dose naloxone. The administration of low dose naloxone was unaccompanied by side effects.

DISCUSSION

This study showed that, after the i.m. administration of morphine there was depression of ventilation and reduced sensitivity to carbon dioxide which lasted for 7 h. The subsequent administration of nalmefene produced a significantly greater change in $\dot{V}_{E}8$ during the final two time periods, that is from 1.5 to 6 h, than did either dose of naloxone. These results were not seen for $P_{E'_{CO_2}}$, for which there appeared to be no difference between nalmefene and high dose naloxone, and nalmefene differed from low dose naloxone only in the middle time period (1.5–4.5 h).

The different effects of these two opioid antagonists on $P_{E'_{CO_2}}$ and $\dot{V}_{E}8$ following morphine may be clinically significant and imply that impaired respiratory control may not be reflected completely in resting $P_{E'_{CO_2}}$ measurements. This impairment is revealed by a carbon dioxide challenge which only nalmefene antagonized throughout the 6-h period of the study.

The change in log slope of ventilatory response to hypercapnia following morphine-induced respiratory depression (fig. 4), confirmed the hypothesis that nalmefene produces prolonged opioid antagonism. The suggestion of some degree of respiratory stimulation by nalmefene above baseline was not confirmed by statistical testing (table III).

Rate of ventilation failed to show any significant change with any drug regimen, lending weight to the belief that ventilatory rate is not related closely to the degree of respiratory depression.

Towards the end of the study period the effect of morphine on ventilation waned and, for this reason, the differences between the groups tended to disappear.

Our results are in keeping with a rather different study by Gal and DiFazio [15], who pretreated subjects either with a placebo or with nalmefene 0.5 mg, 1 mg and 2 mg and then challenged them with the synthetic opioid fentanyl 2 $\mu g\ kg^{-1}$ at intervals for up to 8 h. Their results showed that antagonism persisted for 4 h with the 0.5-mg dose and up to 8 h with larger doses. They also observed a mild respiratory stimulant effect of nalmefene in some subjects before the administration of fentanyl.

Their study has a number of limitations in terms of relevance to clinical practice in that pretreatment with opioid antagonists is rarely used clinically. Furthermore, all the doses of nalmefene in their study caused pharmacological effects that exceeded those produced by the conventional dose of naloxone used in most clinical practice.

One of the problems in the design of our study was to determine the dose of nalmefene that would be equivalent in potency to the standard dose of naloxone 0.4 mg/70 kg body weight. In terms of receptor binding, nalmefene is more effective than naloxone at inhibiting agonist binding at central kappa and delta sites, whilst at central μ sites nalmefene is almost four times as potent as naloxone [9]. In terms of reversing the effects of morphine on tail flick in rats, nalmefene is twice as potent as naloxone (Manufacturers' *Information for Physicians*, 5th Revision 1984). On this basis we assumed that nalmefene was two to four times more potent than naloxone; because nalmefene 0.5 mg was the smallest dose that had been studied previously we decided to compare no more than this dose (in fact nalmefene 0.4 mg) with multiples of the conventional dose of naloxone.

These results are consistent with the properties of the drug [6] in that nalmefene 0.4 mg/70 kg has more potent opioid antagonist activity than both conventional and high-dose naloxone and its duration of activity exceeds 4 h. In this regard, nalmefene 0.4 mg appeared to be comparable to naloxone 1.6 mg during the 0–1.5 h time period, but with a longer duration of action. It would be of considerable interest to study the degree of duration of antagonist activity produced by nalmefene 0.1 mg.

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EXTRADURAL BLOCK WITH BUPIVACAINE: INFLUENCE OF DOSE, VOLUME, CONCENTRATION AND PATIENT CHARACTERISTICS

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SUMMARY

In a randomized, double-blind study the influences of the characteristics of both solution (dose, volume, concentration) and patient (age, weight, height, body mass index) on the development of extradural blockade produced by a low lumbar injection of bupivacaine were investigated. Thirty patients aged between 20 and 50 yr received one of three solutions (groups I–III, respectively): 0.75% 10 ml (75 mg); 0.5% 15 ml (75 mg); 0.75% 15 ml (112.5 mg). A further 20 patients older than 50 yr received 0.75% bupivacaine 10 ml (group IV, n = 10) or 15 ml (group V, n = 10). The number of segments blocked at maximal extent of block was virtually the same in each group: group I (0.75% 10 ml) 13.3 (SD 1.4); group II (0.5% 15 ml) 14.1 (2.9); group III (0.75% 15 ml) 13.8 (2.2); group IV (0.75% 10 ml) 14.2 (2.1); group V (0.75% 15 ml) 16.7 (3.1). The larger dose of bupivacaine (112.5 mg) produced the fastest onset and longest duration of block. Onset and recovery intervals were similar with 0.75% and 0.5% solutions when administered at the same dose (75 mg in 10 ml or 15 ml). There was no correlation between the level of block and the age, weight and height of the patient. In patients who received 15-ml injections, there was a positive association between the upper level of block and body mass index.

Although the technique of extradural anaesthesia was first used in 1921 [1], the factors which determine the spread of local anaesthetic solution within the extradural space remain controversial. Bromage [2–4] identified the dose of drug injected, the age of the patient, the presence of arterial disease and pregnancy as being the dominant factors but, of these, the first three have been disputed [5, 6]. Amongst the other factors said to influence extradural spread are the site and speed of injection, the orientation of the bevel of the needle and the position of the patient [7]. However, it is generally recognized that there is great variability in the level of block even when these factors are standardized. One authoritative source [8] has said of extradural block: "The height of analgesia produced by a given volume of solution is one of the great uncertainties of anaesthesia".

Few, if any, of the studies of extradural anaesthesia have been randomized or double-blind in design and we believe such studies are needed. Therefore, a study was designed to assess the influence of both solution and patient characteristics on the development of blockade produced by the extradural administration of bupivacaine.

PATIENTS AND METHODS

Fifty healthy patients who were to undergo elective surgery for varicose veins under extradural block gave informed consent to the study, which was approved by the local hospital ethics committee. The study was performed in two parts, but a standard anaesthetic technique was used throughout. Patients were premedicated with temazepam 10 mg by mouth 1 h before arrival in theatre. A cannula was inserted to a distal forearm vein, but no fluids were admin-

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istered. The patient was placed in the right lateral position on a horizontal operating table, and a 16-gauge Tuohy needle was inserted at the third lumbar space. The extradural space was identified by the "loss of resistance" technique using as small a volume of saline as possible (< 2 ml). The needle bevel was directed cranially and the bupivacaine solution was injected at 0.5 ml s^{-1}. The needle was then removed and the patient turned to the supine position, with extended legs.

In each patient, the extent of sensory block (analgesia), heart rate, arterial pressure and degree of motor blockade were recorded every 5 min for 30 min after injection, by an observer who was unaware of the nature of the injection. Analgesia was defined as the inability to differentiate the prick of a short-bevelled 26-gauge needle, and touch. If there was a difference in the upper level between the two sides of the body, this was noted and the mean used in the analysis of the results. Motor blockade was assessed using a modified Bromage score: 0 = full movement; 1 = loss of knee extension against gravity; 2 = loss of knee flexion and extension; 3 = total paralysis. Thirty minutes after injection, the patients were sedated with midazolam (up to 10 mg i.v.) and surgery commenced. After surgery, the regressions of sensory and motor blocks were documented hourly.

In the first part of the study 30 patients aged between 20 and 50 yr were randomly allocated to receive one of three injections: group I 0.75% bupivacaine 10 ml (75 mg); group II 0.5% bupivacaine 15 ml (75 mg); group III 0.75% bupivacaine 15 ml (112.5 mg). Each group contained 10 patients and this design allowed comparison of dose (75 mg *v.* 112.5 mg), volume (10 ml *v.* 15 ml) and concentration of solution (0.5% *v.* 0.75%), with the third factor held constant.

In the other part of the study, a further 20 patients older than 50 yr were randomly allocated to receive either 0.75% bupivacaine 10 ml (group IV), or 0.75% bupivacaine 15 ml (group V). The data from these groups were collected for combination with those from groups I and III, respectively, to allow the examination of the influence of patient characteristics on spread.

Randomization was achieved by drawing cards from precoded envelopes. In the analysis of the results statistical methods used were: analysis of variance (ANOV) for multiple group comparisons of spread; *F* test (two groups) or Bartlett test (more than two groups) for between-group comparisons of the variability of spread. Differences in degree of motor block were compared using Kruskal–Wallis test; association of upper level of block with individual patient variables was evaluated by Kendall rank correlation [9].

RESULTS

Demographic data on the five groups of patients are shown in table I and the results of the study are summarized in figures 1–3, and in tables II–IV. The block was adequate for the performance of the projected surgery in every patient.

In the first part of the study, the degree of spread of sensory analgesia was virtually the same in each group. The mean number of spinal segments affected at maximum extent of block in each group was as follows: group I (0.75% 10 ml) 13.3 (SD 1.4); group II (0.5% 15 ml) 14.1 (2.9); group III (0.75% 15 ml) 13.8 (2.2) (ns). Although the variability in spread produced by the 15-ml injection (groups II and III) was greater than with the 10-ml injection (group I), this was not statistically significant (Bartlett test). Since full analgesia of the sacral segments was obtained and there were no "missed" segments below an upper

TABLE I. *Patient characteristics. Mean (SD)*

	Group I 0.75% 10 ml	Group II 0.5% 15 ml	Group III 0.75% 15 ml	Group IV 0.75% 10 ml	Group V 0.75% 15 ml
Age (yr)	37.4 (8.1)	37.2 (9.1)	37.6 (6.3)	60.8 (5.4)	57.7 (5.6)
Weight (kg)	71.7 (16.9)	62.2 (8.7)	68.8 (13.6)	70.3 (9.6)	70.1 (12.1)
Height (m)	1.67 (0.12)	1.66 (0.08)	1.70 (0.83)	1.67 (0.05)	1.69 (0.10)
BMI (kg m^{-2})	25.4 (3.8)	22.3 (1.9)	23.7 (3.1)	25.1 (4.5)	24.9 (3.5)
F:M	9:1	7:3	7:3	7:3	7:3

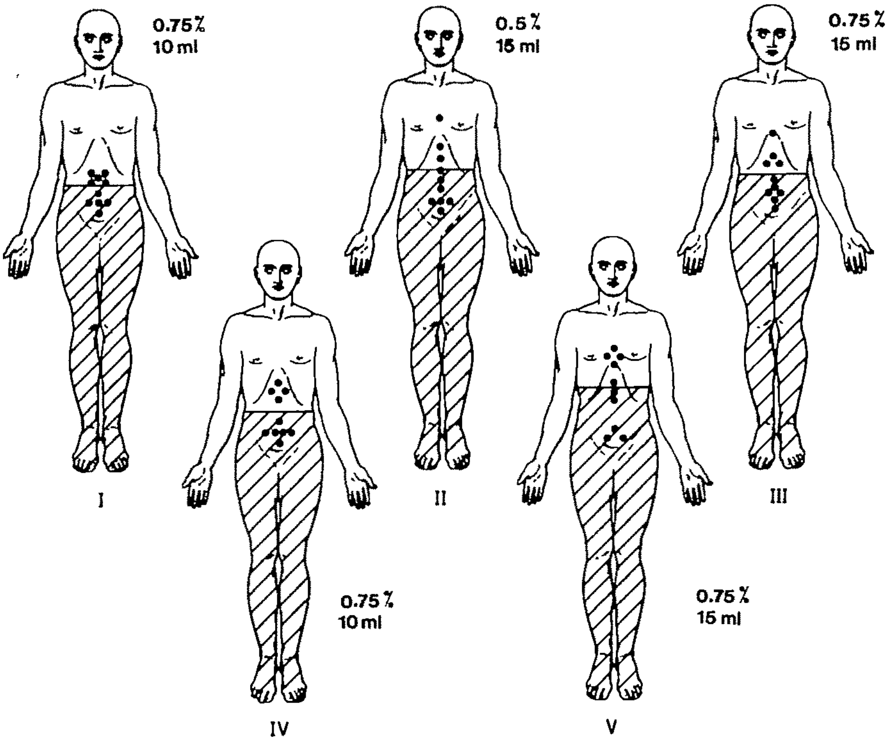

FIG. 1. Extent of extradural block in the study groups. Each symbol represents the maximum spread of analgesia in one patient. The mean level of spread in each group is shown by the upper extent of the shaded area.

sensory level, the number of segments blocked was directly related to the upper level of block. The results for individual patients are shown in figure 1. Variability in spread is reflected in the range of block observed in each group: group I T12–T8; group II T12–T3; group III T11–T4. Differences of more than two spinal segments in the upper level of block on the two sides of the body were seen only in patients who received a 15-ml injection; that is in two patients in group II (T5/L1; T8/T4), and in four patients in group III (T9/T6; T6/T3; T9/T5; T9/T12).

There were obvious differences in the onset of sensory block. The time to detection of analgesia at the T12 dermatome was significantly shorter in group III, who received the larger dose (112.5 mg), than in groups I or II, who received the smaller dose (75 mg) in either 10 ml (0.75%) or 15 ml (0.5%) of solution. Comparing groups I and II in this respect, the mean time to onset at T12 was shorter after the more concentrated solution, but this difference was not statistically significant.

Although there was a suggestion that the larger dose of bupivacaine also produced a greater degree of motor block (table II), there was no statistically significant difference between the groups. Only one patient (in group I) developed total motor blockade.

Changes in heart rate and arterial pressure during the first 30 min were minimal (table III). No patient required treatment for hypotension at any time during the study period or during the subsequent surgical procedure.

The dose of bupivacaine administered had the greatest effect on the duration of both motor and sensory block (table II). The mean times to regression of sensory analgesia to T12, and to complete recovery from sensory block, and to recovery of the ability to raise a straight leg were similar in groups I and II, but longer in group III. Statistical significance was achieved in the comparison of group III with groups I and II in respect of time to complete recovery from sensory block, and in the comparison of group III and group I in respect of recovery from motor block.

Apart from being older, the patients in groups

TABLE II. *Onset and recovery characteristics. Comparison with group III*: *P < 0.05 (*ANOV*)

	Group I 0.75% 10 ml	Group II 0.5% 15 ml	Group III 0.75% 15 ml
Sensory block (mean (SD))			
Time to onset of analgesia at T12 (min)	14.5* (4.7)	17.0* (2.6)	9.5 (3.4)
Time to regression of analgesia to T12 (h)	4.2 (0.9)	4.3 (0.9)	4.9 (0.9)
Total duration of sensory block (h)	5.3* (1.2)	5.0* (1.3)	6.6 (1.3)
Motor block (No. patients)			
Bromage score at 30 min			
0	2	2	2
1	7	7	3
2	0	1	5
3	1	0	0
Time to recover ability to raise straight leg (min)	3.9* (0.6)	4.2 (0.6)	4.9 (0.9)

TABLE III. *Cardiovascular responses. Mean change (range) from control values in systolic arterial pressure and heart rate recorded at 10, 20 and 30 min after injection*

	Systolic arterial pressure (mm Hg)			Heart rate (beat min^{-1})		
	Group I 0.75% 10 ml	Group II 0.5% 15 ml	Group III 0.75% 15 ml	Group I 0.75% 10 ml	Group II 0.5% 15 ml	Group III 0.75% 15 ml
10 min	−7.7 (+15 −30)	+1.8 (+10 −7)	−7.4 (+5 −20)	−2.0 (+13 −14)	−1.0 (+22 −17)	−2.3 (+24 −13)
20 min	−6.0 (+25 −25)	−1.2 (+10 −17)	−9.9 (+5 −25)	−5.7 (+4 −13)	−0.8 (+22 −12)	−1.8 (+16 −13)
30 min	−5.6 (+22 −25)	−2.9 (+8 −20)	−9.2 (0 −25)	−5.0 (+3 −12)	−1.2 (+18 −18)	+1.2 (+16 −20)

IV and V were similar to those in groups I and III and the blocks that were produced were also very similar to those seen in the younger patients (fig. 1). The mean maximum number of spinal segments blocked was: 14.2 (SD 2.1) in group IV (0.75% 10 ml) and 16.7 (3.1) in group V (0.75% 15 ml). This difference was not statistically significant, nor were the differences between these two groups and the younger patients who received the same injection (groups I and III). Again, there was a tendency for the 15-ml injection to produce a wider range of blocks than the 10-ml but, even when the data from the groups I and IV and groups III and V were combined before analysis, no statistically significant differences were detected (*F* test).

To assess the association of patient characteristics with extradural spread, the data from groups I and IV (0.75% 10 ml; $n = 20$) and groups III and V (0.75% 15 ml; $n = 20$) were combined. For each patient the upper level of block produced was plotted against patient age, height, weight and body mass index (BMI = weight/height^2 (kg m^{-2})) (figs 2, 3). Kendall rank correlation coefficients (table IV) were calculated to indicate any association of these variables with spread.

TABLE IV. *Association of height of sensory block with four patient variables for 10-ml and 15-ml injections of 0.75% bupivacaine: age; height; weight; BMI. Kendall Rank Correlation coefficient.* *P < 0.05

	0.75% 10 ml (A) ($n = 20$)	0.75% 15 ml (B) ($n = 20$)	Combined (A+B) ($n = 40$)
Age (yr)	+0.17	+0.28	+0.18
Weight (kg)	+0.05	−0.11	−0.01
Height (m)	+0.13	+0.27	+0.18
BMI (kg m^{-2})	+0.14	+0.41*	+0.22

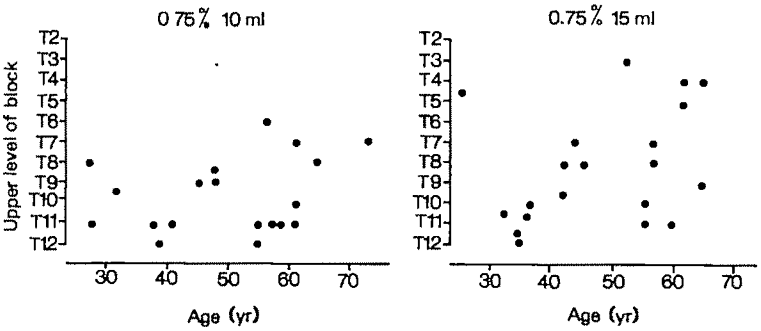

FIG. 2. Patient age plotted against maximum extent of block in all patients receiving 10 ml ($n = 20$) and 15 ml ($n = 20$) injection of 0.75% bupivacaine plain.

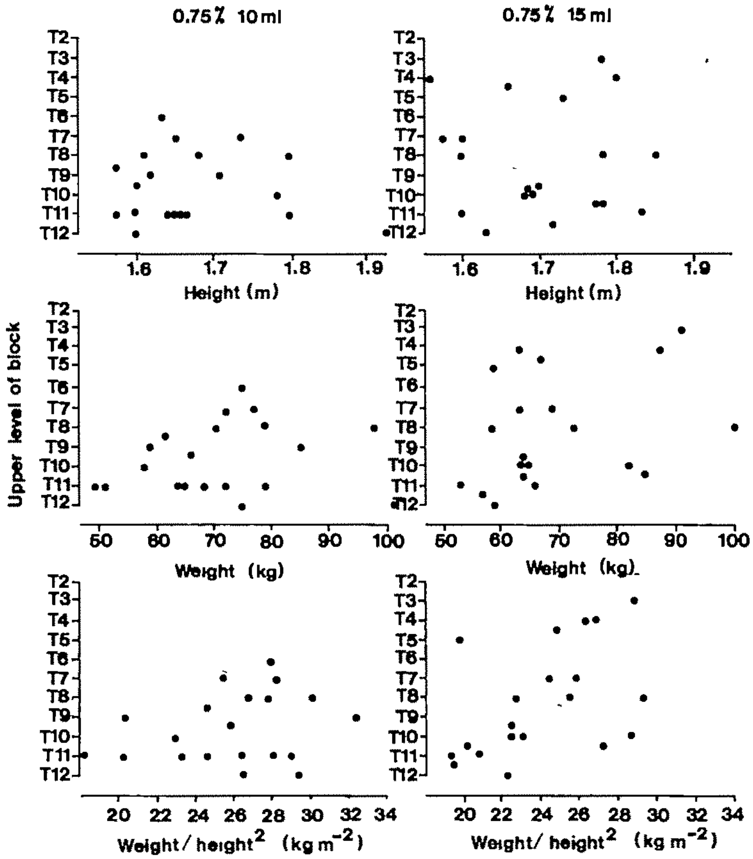

FIG. 3. Patient characteristics (age; weight; height; weight/height^2) plotted against maximum extent of block in all patients receiving 10 ml ($n = 20$) and 15 ml ($n = 20$) injections of 0.75% bupivacaine plain.

The only statistically significant association was with BMI, which appeared to have a weak influence on spread, but only with the larger dose of bupivacaine (0.75% 15 ml).

DISCUSSION

The features of any local anaesthetic solution that may influence extradural blockade are the volume, concentration and the product of these two, the dose of drug. A problem of interpreting the results of most studies that have attempted to characterize the effect of any one of these factors is that changes in the variable under study have automatically produced changes in another. For instance, if two concentrations are compared, but the same volume is injected, there is a concomitant increase in dose of drug administered [10]. The design of this randomized, double-blind study allowed the influence of each factor to be examined separately.

The results showed that, with low lumbar injection of bupivacaine, the single most important factor was dose of drug. The larger dose produced a faster onset and a longer duration of action. There was also a suggestion that, at the same dose (75 mg), the more concentrated solution produced a more rapid onset than the more dilute one, but the difference was not statistically significant. The most intriguing result was that the degree of spread observed in each of the groups was virtually the same, in spite of the differences in the characteristics of the solutions used. An interesting point, worthy of further study, was that the smaller volume appeared to produce less variable blocks. The range in upper sensory level was smaller in patients who received 10-ml than in those who received 15-ml injections, and instances of asymmetric blocks were only observed with the larger volume. However, even when the data of the young and older patients who received the same volume and concentration of solution were combined, the numbers studied were not sufficient for the differences in range of blocks to achieve statistical significance. If this result was to be confirmed by a larger study, it would suggest that the most predictable extradural block would be produced by a low volume of a concentrated solution. A similar finding has been obtained for intrathecal injection [11].

These results contradict a number of widely held beliefs, particularly that spread is related to both the volume and the dose injected. The numbers studied were small, and the maximum volume used was only 15 ml, but the results are supported by the much larger open study of Grundy and colleagues [5]. They collected clinical information on 334 lumbar extradural blocks performed with 10, 15 or 20 ml of 0.75% plain bupivacaine. They found that this stepwise increase in dose and volume did result in an increase in spread, but only by a relatively small degree. From a mathematical model based on their data they predicted that, for a 60-yr-old man of average build, a doubling of the volume of injection from 10 to 20 ml would be reflected in an increase in cephalad spread of only three to four segments.

Much of the early work on extradural spread was with lignocaine and it might be that there are differences between drugs. However, Park and colleagues [6] also found that there were only small differences in spread in 270 patients who received lumbar blocks with either 10, 15 or 20 ml of 1.5% lignocaine with adrenaline. Szeinfeld and colleagues [12] have shown a correlation between spread and the volume injected for extradural blood patch, but blood is a fluid with characteristics very different from those of a local anaesthetic solution. Spread was observed for 3 h, but a local anaesthetic solution would be absorbed into either the circulation or the extradural tissues long before that time, so it is unlikely that it would spread in a similar way.

When the upper level of block was related to the characteristics of the patients who received either 10 or 15 ml of 0.75% bupivacaine, there was no demonstrable correlation with patient age, weight or height. There was some positive association of spread with body mass index, but only in those patients who received the 15-ml injection ($P < 0.05$). Increased spread in obese patients has been reported after intrathecal injection [13]. Since this finding was not apparent after the injection of 10 ml, a stronger association between spread and BMI with larger volumes may, in part, explain the tendency to greater variability in upper level of block observed in the patients who received 15 ml. With regard to age, these results are at variance with those of Bromage [4] who found a strong positive association between age and spread, but other work has also disputed this. Park and colleagues [6] found that spread was slightly greater in patients older than 40 yr than in those who were between 20 and 39 yr, but that there was virtually no difference in spread between the 40–59, 60–79 and > 80 yr groups. Grundy and colleagues [5] found that age had some influence on spread, but that the degree of this effect was minor. Another recent study has also confirmed this lack of association with age [14].

A striking feature of this study was the quality and symmetry of the blocks that were produced. Problems of "missed" segments and unilateral blocks were not seen, and perhaps this was because an extradural catheter was not used. Although the level of block was suitable for lower limb surgery in every patient, there would have been a similar, and unacceptably large, failure rate in each group had the block been intended for lower abdominal surgery (fig. 1). The implication of the results is that injecting a larger volume at low lumbar level is not a reliable method of increasing cephalad spread. It may be more appropriate to change the site of injection so that it matches the dermatomal level of the operation, and this feature of the extradural technique has been appreciated since its early use [15]. It seems likely that the factors governing spread of solution injected at other levels would be similar, but this will require confirmation by clinical trial.

Another interesting feature of the study was the circulatory stability of the patients. No patient required any kind of treatment for hypotension at any time, yet the changes in arterial pressure were minor. Similar studies of intrathecal anaesthesia are associated with a significant incidence of hypotension. Two factors are certainly relevant. First, the block spread above T6 in relatively few patients, so there was little effect on the sympathetic innervation of the heart. Second, when block spread to that level it took 15–20 min to do so. This would allow time for the circulation to compensate for sympathetic blockade. After intrathecal injection of many local anaesthetic solutions, the block spreads to a high level more rapidly and more often.

Most anaesthetists consider that concentration of solution is the prime determinant of the quality of an extradural block (rate of onset, degree of motor block, duration), and that drug dosage is more important in relationship to systemic toxicity. In the first part of this study, a three-way comparison of the effect of independent changes in concentration, volume and dose of bupivacaine was performed. It was found that dose was the most important determinant of the block. Concentration had some influence on rate of onset, but the effect was not statistically significant under the conditions of the study. An aspect of increasing drug concentration worthy of further investigation was that the decrease in the volume of injection that it allowed suggested that more consistent blocks were produced. Mean spread was little influenced by any of these factors, and the only patient factor examined that was found to correlate with individual variation in block height was degree of obesity.

This study was performed in patients who received extradural injection without the placement of a catheter. We feel that the single injection extradural technique used here is one that merits re-evaluation. It cannot be assumed that the findings of this study would apply necessarily to the more widely used multiple injection catheter technique.

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MATERNAL–FETAL DISTRIBUTION OF BUPIVACAINE IN THE RABBIT

R. J. CARSON AND F. REYNOLDS

It has long been established that fetal:maternal plasma concentration (F:M) ratios of bupivacaine are relatively low at delivery following extradural analgesia [1]. It has been claimed that such low ratios might result from extensive tissue uptake [2], rather than slow placental transfer, even though ratios do not increase consistently with dose–delivery interval [3], as would be expected during tissue equilibration. Rabbit placental perfusion experiments have demonstrated consistently slow transfer of bupivacaine, associated with high maternal protein binding [4–6], but these experiments cannot measure tissue uptake or equilibration. Progressive accumulation of bupivacaine in brain and other tissues on prolonged maternal administration might result in serious detriment to the offspring. In order to establish if such accumulation does occur, we have examined in rabbits the uptake of bupivacaine in feto–placental units removed serially during maternal steady-state infusion. A brief report of part of this work has appeared elsewhere [7].

SUMMARY

Bupivacaine was infused i.v. in nine anaesthetized pregnant rabbit does near term. Pups were removed at 10–15 min intervals and bupivacaine concentrations measured in fetal plasma, brain, placenta, amniotic fluid, maternal plasma sampled synchronously and maternal brain at the end of the experiment. Mean maximum fetal:maternal (F:M) ratio was 0.31 (SD 0.16) (range 0.18–0.64). Mean fetal brain:plasma ratios ranged from 2.04 to 5.09. There was no progressive increase in fetal brain bupivacaine concentration with time. Maternal brain:plasma ratio was 1.62 (0.81). However, maximum fetal brain concentration was only 0.27–0.86 of maternal. Concentrations increased with time in amniotic fluid, but did not exceed those in maternal plasma. Although there was some accumulation of bupivacaine in rabbit fetuses, tissue uptake could not account for low F:M ratios persisting beyond 80 min.

MATERIALS AND METHODS

The experiments were conducted on nine pregnant New Zealand white rabbits (weights 3.8–4.9 kg (mean 4.4 (SD 0.4) kg) within 4 days of term (gestation = 30 days). The does were anaesthetized using alphaxalone/alphadolone and urethane as described previously [6] and they breathed air spontaneously through a tracheostomy. A carotid artery was cannulated for monitoring of arterial pressure and sampling. Bupivacaine 1.25 mg ml^{-1} was infused into a neck vein at a rate of 12 ml h^{-1} for 20 min as a loading dose, followed by 6 ml h^{-1} for 1 h, then 3 ml h^{-1} thereafter. Single fetal sacs were removed through a series of hysterotomies at intervals of approximately 15 min, sampling maternal plasma synchronously on each occasion. The first fetal sac was removed 6–20 min after the start of the maternal infusion of bupivacaine, except in two does, when it was delayed for 72 and 77 min to allow time for fetal equilibration in the absence of maternal insults. Amniotic fluid was collected, each fetus decapitated and blood collected via a funnel into a heparinized tube; the placenta and the brain were removed and weighed. The maternal brain was removed likewise at the end of the experiment.

All tissues were homogenized in hydrochloric acid 0.1 mol $litre^{-1}$ using an Ultraturax homogenizer. Homogenate volumes were between 7.5

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TABLE I. *Physiological data (mean (SD)). MAP = mean arterial pressure*

	Initial	Final	*P*
MAP (mm Hg)	93.0 (15.0)	72.0 (14.0)	< 0.01
pH	7.487 (0.040)	7.386 (0.145)	ns
Pa_{O_2} (kPa)	10.2 (2.3)	9.5 (3.4)	ns
Pa_{CO_2} (kPa)	2.9 (0.6)	2.5 (1.0)	ns

TABLE II. *Weight of does, fetuses and tissues (mean (SD))*

	Weight	
	Mean (SD)	Range
Doe (kg)	4.39 (0.38)	3.80–4.91
Fetus (g)	23.3 (6.7)	12.3–37.4
Placenta (g)	3.9 (1.3)	1.9–7.1
Fetal brain (g)	0.5 (0.1)	0.1–0.8

and 20 ml, and 2.5-ml samples were assayed. Bupivacaine concentrations were measured in all samples of tissue, amniotic fluid (0.5 ml) and plasma (0.1–0.5 ml) by gas–liquid chromatography following a three-stage extraction process, and using a nitrogen detector, with 1-ethyl-2′, 6′-pipecolylxylidine as internal standard. Maternal arterial pH and blood-gases were analysed before and after the removal of all fetal sacs. Results are expressed where appropriate as mean (SD). Student's *t* tests (paired and unpaired) were used to test for significant differences between means. Reciprocals of concentration and time were calculated in order to determine the time to 50% equilibration into amniotic fluid.

RESULTS

There was a significant reduction in mean arterial pressure, but not pH or blood-gas values, between the beginning and end of the experiment (table I). Does had between four and 11 fetuses (mean 8). The weights of the does, pups, placentae and brains are shown in table II.

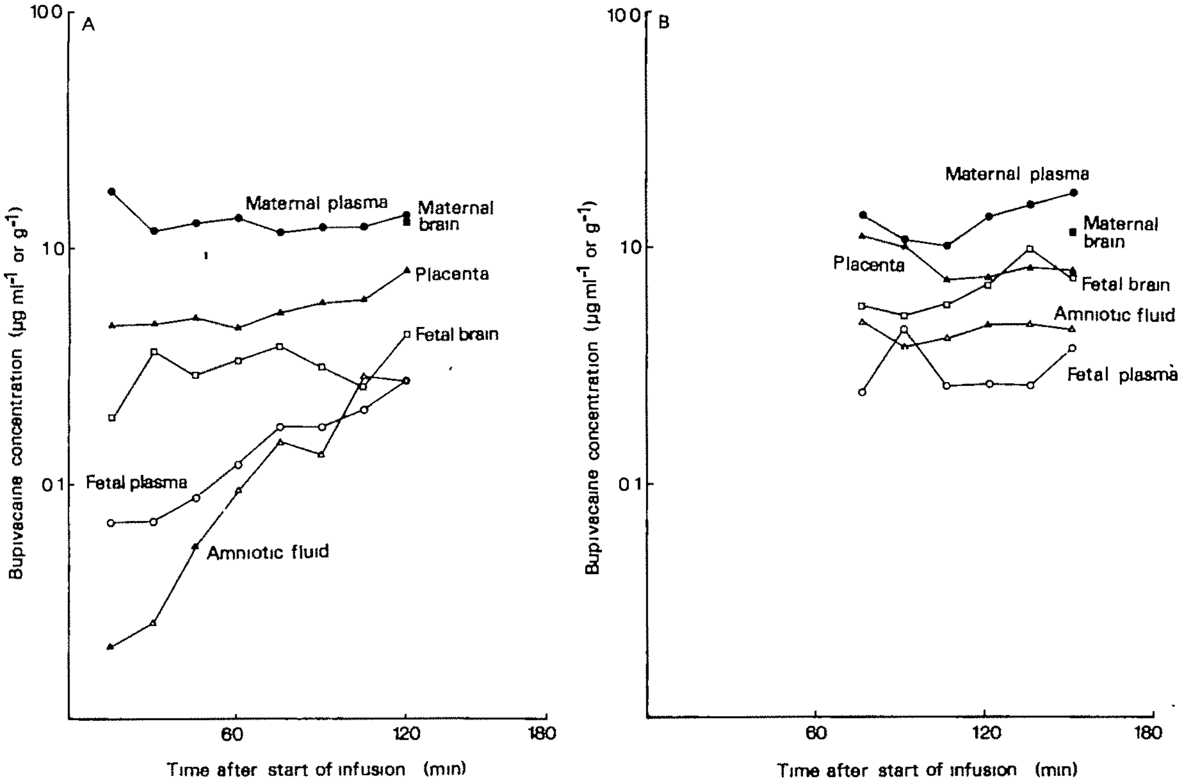

FIG. 1. Concentrations of bupivacaine (logarithmic scale). A: Fetal sampling started 15 min after the beginning of the infusion of bupivacaine. B: Sampling delayed for 77 min.

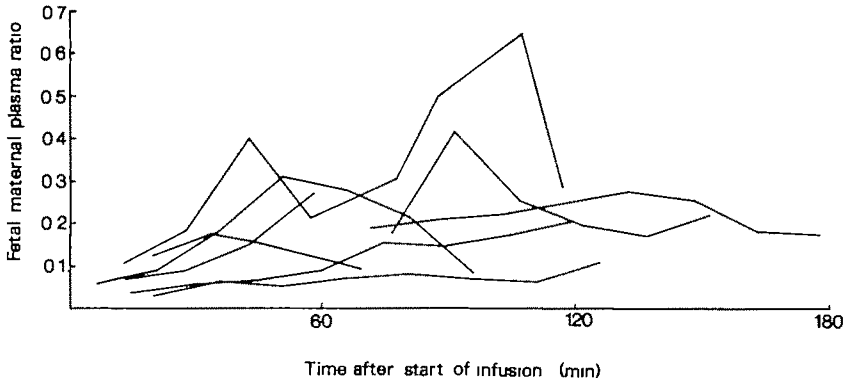

FIG. 2. Fetal:maternal plasma concentration ratios of bupivacaine ($n = 8$). In the first experiment, maternal blood samples were not drawn at each fetal sampling. Note that, in two experiments, the start of sampling was delayed.

The intrapair correlation for duplicate bupivacaine analyses was > 0.99 ($n = 35$). Coefficient of variation for the assay was 5%.

Figure 1 shows typical data, from a single doe and her fetuses, and data from one of the does in which sampling was delayed. Bupivacaine concentration was consistently higher in maternal plasma than that in any fetal compartment.

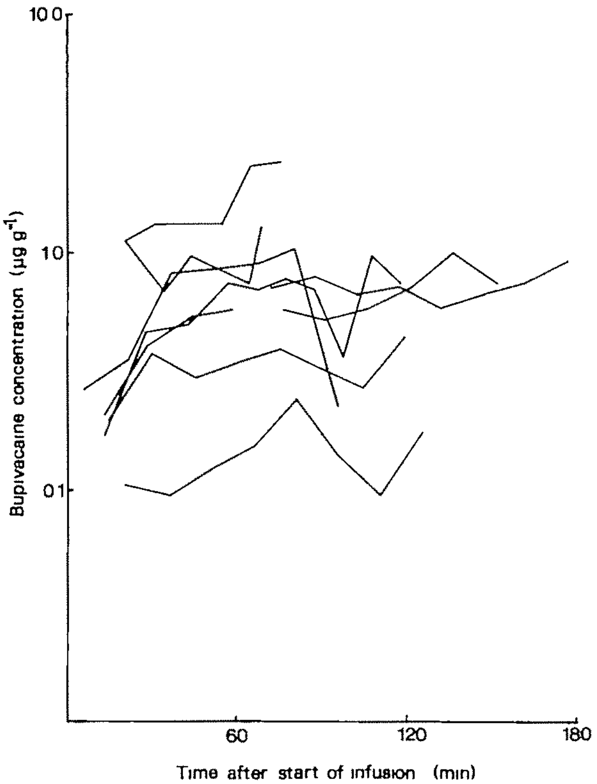

FIG. 3. Fetal brain concentrations of bupivacaine (logarithmic scale) ($n = 9$).

Individual F:M ratios (fig. 2) all increased for the first 30–40 min and thereafter there was no consistent trend. The mean (SD) *maximum* F:M ratio was 0.31 (0.16) and the range 0.18–0.64.

Fetal brain concentration (fig. 3) also increased initially in five of the seven animals sampled early, again with no consistent changes thereafter. *Maximum* fetal brain bupivacaine concentration in a given litter ranged from 27 to 86% of the doe's brain concentration. The highest fetal brain concentration occurred at 58–178 min from the start of the infusion (mean 101 (39)). Fetal brain:plasma ratio ranged from 1.1 to 6.5 (means 2.0–5.1) and did *not* increase with time but demonstrated, if anything, a downward trend (fig. 4). The mean *maximum* fetal brain:plasma ratio was 4.8 (1.3) and was significantly greater ($P < 0.001$) than the mean maternal brain:plasma ratio of 1.6 (0.8) (range 0.68–3.1).

Placental bupivacaine concentration increased in five does for between 30 and 80 min, but otherwise showed no marked changes (fig. 5). Only bupivacaine concentrations in amniotic fluid showed a clear upward trend, and appeared to plateau at approximately 90 min (fig. 6) (time to half maximum = 27.6 min).

DISCUSSION

Rabbits were selected as the experimental model because progressive fetal tissue accumulation could be measured by making use of the large

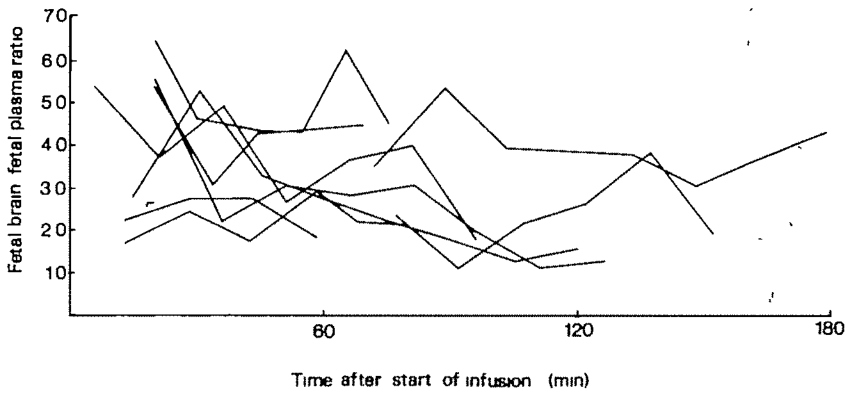

FIG. 4. Fetal brain:plasma ratios (n = 9).

litters. This advantage was thought to outweigh the inconvenience of small fetal plasma volumes.

A degree of accumulation was noted in the rabbit fetal compartment, but it was not sufficient to explain observed low F : M plasma ratios which, although sometimes erratic, mostly remained less than 0.3. The occasional high values shown in figure 2 may be explained by the presence of acidosis in some pups, which would promote ion trapping in fetal plasma. Kennedy and col-

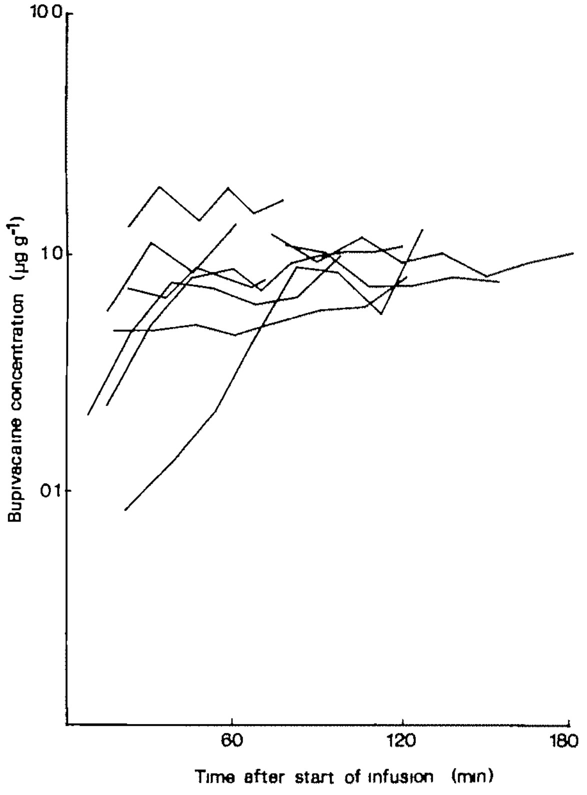

FIG. 5. Placental concentrations of bupivacaine (logarithmic scale) in all does.

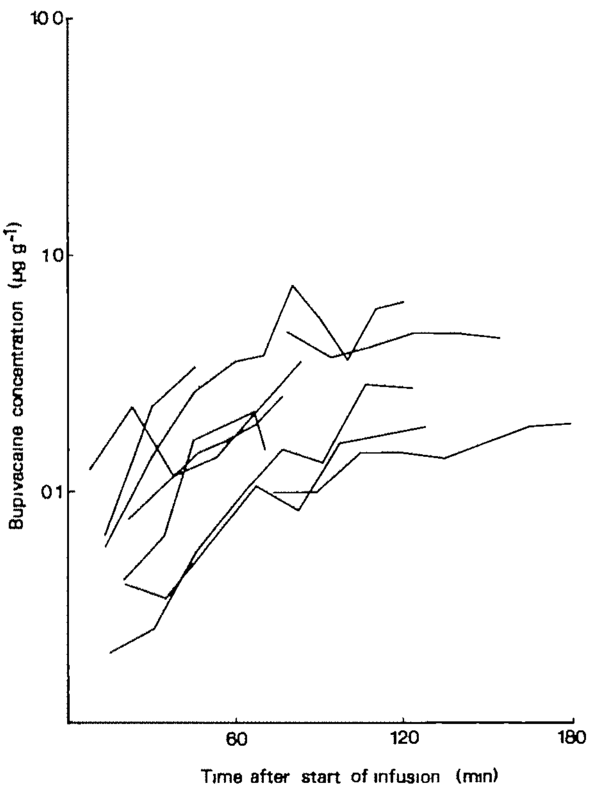

FIG. 6. Amniotic fluid concentrations of bupivacaine (logarithmic scale) in all does.

leagues [8] demonstrated a significant increase in F:M bupivacaine ratio in the presence of an increased transplacental pH gradient, in sheep. While the does themselves were not acidotic in the present study, and their circulations not greatly impaired by anaesthesia, repeated hysterotomy and removal of conceptus (table I), it was impossible to ensure that all *fetuses* were not acidotic. Indeed, the variation in size among litter mates attests to the variability in function among the placentae. It was not possible to measure fetal plasma pH because all the small volume of fetal blood available was required for analysis of bupivacaine, and because the method of collection precluded it. It was to eliminate the possible effect of repeated maternal insults on long term distribution of bupivacaine that removal of conceptuses was delayed in two experiments, when bupivacaine concentrations were observed to be reasonably stable in all compartments (figures 1B, 3 and 5).

Using the sheep model, Kennedy and his associates [9] found that mean F:M bupivacaine ratios increased progressively to approximately 0.3 after 1 h of maternal infusion with no significant difference at that time between umbilical venous (UV) and fetal arterial (FA) concentrations, suggesting little continuing uptake. After infusion was stopped, F:M ratios increased further and FA exceeded UV, denoting back transfer despite F:M ratios of 0.3–0.5. It is now well established in humans that low F:M bupivacaine ratios at delivery following extradural administration are associated with reduced protein binding in the fetus, with negligible gradient for free drug [10, 11]. The concentration of the principal binding protein for bupivacaine, α_1-acid glycoprotein, is lower in fetus than mother, even at term, in both man [12] and rabbit [5].

Fetal brain concentration of bupivacaine exhibited no consistent upward trend, and indeed fetal brain:plasma ratio appeared to decline with time. This may be explained by the superior buffering power of the brain in the face of systemic acidosis. A study in non-acidotic, non-pregnant mice [13] has confirmed a constant relationship between blood and brain concentrations of bupivacaine at 2–40 min following bolus i.v. injection. Indeed, in mice, there was no evidence of significant tissue uptake of bupivacaine beyond 2 min into any of the vessel-rich group.

Of the compartments examined in the present study, the only one showing any evidence of slow accumulation of bupivacaine was amniotic fluid. Drugs which undergo rapid renal excretion appear quickly in amniotic fluid following placental transfer [14]. For a lipid soluble drug such as bupivacaine (partition coefficient in oleyl alcohol/pH 7.4 buffer = 257 [4]), in which renal excretion of unchanged drug plays only a small part in elimination [15], the amniotic fluid represents a very slow compartment, which probably equilibrates directly with the maternal compartment across the amnion [14].

Being lipid soluble, bupivacaine accumulates in fat, but more slowly than in the vessel-rich group of tissues. The fetus, however contains too little fat from which to extract bupivacaine.

In the present study there was no trace of pipecolylxylidine, the initial metabolite of bupivacaine, in any fetal tissues. It does not seem likely, therefore, that metabolism of bupivacaine could contribute to the low concentrations found in the fetus.

Low fetal plasma binding may account for the fact that brain:plasma ratios of bupivacaine were higher in the fetus than in the mother. Nevertheless, fetal brain concentrations rarely exceeded maternal plasma or brain concentrations. Brain concentrations are a determinant of bupivacaine toxicity and it is clear that, in rabbits, bupivacaine does not accumulate in fetal brain during continuous maternal administration. These findings do not support the concept that there might be clinically important accumulation of bupivacaine in fetal tissues as a result of prolonged administration of the drug to the mother.

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ANATOMICAL VARIATION IN THE POSITION OF THE PROXIMAL INTERCOSTAL NERVE

P. A. J. HARDY

SUMMARY

Anatomical study of the proximal intercostal nerve in cadavers revealed three nerve forms, depending on the relation between the nerve and adjacent ribs. This was found in the classical subcostal position in 16.6%, in the midzone in 73% and in the inferior supracostal position in 10%.

Intercostal nerve block with local anaesthetic provides good analgesia which may be extended by the use of intercostal catheters or alternative techniques such as cryoanalgesia. The classical anatomical description is of a segmental nerve lying in the subcostal groove on the lower border of the corresponding segmental rib, adjacent to the intercostal artery and vein [1]. The method of nerve block depends on walking a needle off the lower border of the rib to enter the subcostal groove. Using this technique with percutaneous cryoanalgesia Conacher [2] obtained poor results and suggested that this may have resulted from incomplete contact between the tip of the probe and the nerve.

A major requirement for successful cryoanalgesia is accurate location of the nerve. This study was performed to assess the position of the proximal intercostal nerve in cadavers.

METHODS AND RESULTS

Thirty cadavers were studied in the Medical Dissecting Room in the Department of Anatomy in Liverpool. Thoracic evisceration had been completed, leaving the posterior mediastinum and chest wall complete. The 2nd to 11th intercostal nerves were dissected and followed from the intervertebral foramen to approximately 3–5 cm lateral to the angle of the rib on both sides of the chest wall. After identification of the nerve, the borders of adjacent ribs were located using a blunt probe in order to assess relative position.

From the paravertebral space to the angle of the rib, the nerve lies just below the parietal pleura. From the angle of the rib laterally the internal intercostal muscle lies internal to the intercostal nerve. This muscle was removed to allow the nerve to be followed laterally. The first major division of the nerve starts at about the angle of the rib.

Three forms of intercostal nerve were identified

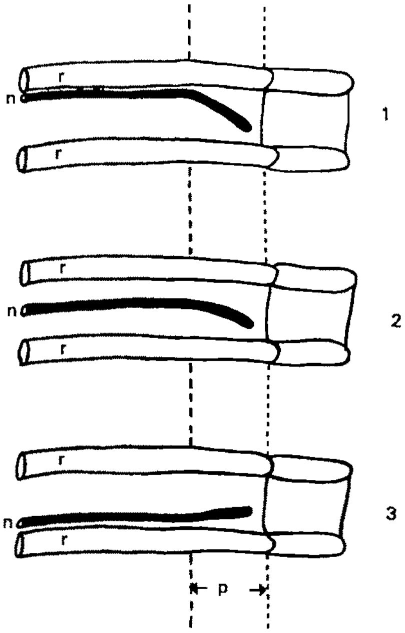

FIG. 1. Diagrams of the observed relations of the intercostal nerve. This shows the nerves (n), ribs (r) and paravertebral spaces (p). 1 = Subcostal relation; 2 = midzone position; 3 = supracostal relation.

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according to the relative position of the nerve and adjacent ribs. The particular form adopted was present in all nerves on both sides in each cadaver. The three identified forms were classical subcostal, midzone and inferior supracostal (fig. 1). As the individual nerve arises from the intervertebral foramen, its position is relatively closer to the inferior rib than to the segmental but superior rib. The adoption of the particular nerve form occurred within the paravertebral space.

The frequency of the individual forms was classical subcostal 16.6% ($n = 5$), midzone 73% ($n = 22$) and inferior supracostal 10% ($n = 3$).

COMMENT

The normal technique of intercostal nerve injection is to insert a needle to produce contact with the appropriate rib and then "walk" the needle off the lower border of the rib. The needle enters the subcostal groove adjacent to the segmental artery and vein. From a single needle insertion the superior intercostal space may be entered also by "walking" the needle off the superior border of the rib.

Injection studies in man have demonstrated that extensive spread of local anaesthetic solution occurs into adjacent intercostal spaces [3, 4] and medially into the paravertebral space [5]. Accurate location of the nerve is not essential with such wide spread of injectate. Interestingly, studies in cadavers reported from North America have demonstrated spread along the injected space, but no spread of injectate across the ribs occurred [6, 7]. This probably represents a difference in injection techniques and not an anatomical variant.

In contrast to injection methods, successful cryoanalgesia depends on placing the tip of the probe in contact with the nerve. Direct vision intercostal cryoanalgesia performed peroperatively produces significant analgesia with fewer respiratory complications [8]. Percutaneous intercostal cryoanalgesia performed using conventional techniques resulted in significant failure rate [2]. The present study showed that the intercostal nerve does not commonly lie in the subcostal groove—and in fact did so in only 16% of cadavers. This explains the failure to locate the nerve using a standard block technique. Post-thoracotomy intercostal neuralgia may be a result of various causes including neuropraxia, neurotmesis and the presence of direct nerve suture [9].

It is interesting to note.the similarity between the frequency of subcostal nerve position (16%) and the incidence of intercostal neuralgia occurring after insertion of Tuohy needles into the intercostal space by a subcostal approach (10%) [5]. This complication should, therefore, be considered when large diameter needles are inserted into the intercostal space to permit cannulation techniques.

In conclusion, significant variation in "normal" anatomy exists and this may result in failure of regional analgesic techniques based on conventional teaching of anatomy. This is particularly the case when techniques such as cryoanalgesia are performed. This variation does not influence conventional local anaesthetic techniques.

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PROPHYLACTIC EXTRADURAL BLOOD PATCH IS EFFECTIVE

A Preliminary Communication

T. G. CHEEK, R. BANNER, J. SAUTER AND B. B. GUTSCHE

SUMMARY

Ten obstetric patients received 17–20 ml of autologous blood through an extradural catheter after inadvertent dural puncture. The time interval from dural puncture to prophylactic extradural blood patch ranged from 90 to 660 min. One of the 10 patients developed a mild occipital headache, which required no further intervention.

Extradural blood patch (EBP) is currently the accepted and definitive therapy for post-lumbar puncture cephalalgia. However, there has been considerable debate on the use of this technique prophylactically. Several investigators have reported conflicting results. Loeser and colleagues [1] reported a 71% failure rate in the first 24 h, while Palahniuk and Cumming [2] claimed a 54% failure rate following an immediate prophylactic EBP. Both of these investigators injected a maximum of 10 ml of blood. Quaynor and Corbey [3] reported a series of 10 non-obstetric patients in whom a prophylactic blood patch was performed within 15 min of accidental dural puncture. They proposed that the 100% success rate was achieved partly because of injection of blood via the extradural needle as opposed to the extradural catheter. Ackerman and Colclough [4] performed immediate prophylactic EBP through the extradural catheter in five patients, and reported 100% success rate.

The purpose of this study was to determine the efficacy of an immediate prophylactic EBP injected through the extradural catheter, with a variable interval between dural puncture and prophylactic blood patch. The time of EBP coincided with both the end of the obstetric procedure and further requirements for analgesia.

METHODS AND RESULTS

Four patients undergoing Caesarean section and six patients in labour received inadvertent dural puncture with an 18-gauge Hustead needle. In all 10, an extradural catheter was inserted immediately one interspace above the previous puncture site. None of the patients was febrile or had signs of systemic infection. The patients requiring Caesarean section received 0.5% bupivacaine 30–35 ml, pethidine 30–35 mg, and morphine (Duramorph) 5 mg through the extradural catheter. Patients in labour received 0.25% bupivacaine 10–12 ml followed by a continuous infusion of 0.125% bupivacaine at a rate of 8–12 ml h^{-1}. The six patients in labour were instructed to push with contractions when the cervix reached 10 cm dilatation. In these six patients, duration of the second stage of labour ranged from 15 to 55 min. Two patients required forceps delivery. Before the patient left the delivery room, 17–20 ml of autologous blood was obtained by aseptic technique and injected via the extradural catheter as rapidly as possible—this was accomplished in 2–3 min. The blood was injected easily using two sequentially drawn 10-ml syringes via a multiport, lateral-eye extradural catheter. Injection was stopped temporarily if the patient complained of back pain, then continued after a brief pause. There was a variable interval between the initial dural puncture and delivery; the interval between dural puncture and prophylactic EBP varied from 90 to 660 min.

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TABLE I. *Patient data and results. L+D = Labour and delivery. C-section = Caesarean section*

Patient No.	Procedure	Quantity of blood (ml)	Time (min) puncture to patch	Headache	Remarks
1	L+D	18	660	No	—
2	L+D	17	90	No	Transient backache
3	C-section	18	140	No	—
4	L+D	18	210	No	—
5	L+D	19	125	No	Transient backache
6	C-section	20	185	No	—
7	L+D	18	265	No	Transient backache
8	C-section	18	165	No	—
9	C-section	19	145	Yes	—
10	L+D	20	280	No	—

Following extradural injection of blood, the patient was maintained in the supine position for 30 min and then instructed to limit activity to bathroom visits only for a subsequent 2–3 h. Assessment of the patients was undertaken at two postoperative visits and by telephone contact.

None of the six labour and delivery patients developed post-lumbar puncture cephalalgia. One of the four Caesarean section patients developed mild occipital headache. This patient was able to walk comfortably, and left hospital symptom free at her scheduled time of discharge without further therapy. All patients were questioned regarding side effects, which were limited to three transient mild backaches, one of which persisted for approximately 2 weeks (table I).

COMMENT

Our findings are consistent with the studies of both Quaynor and Corbey [3] and Ackerman and Colclough [4], and suggest that prophylactic extradural blood patch does reliably prevent post-lumbar puncture cephalalgia.

A critical factor in assuring successful prophylactic EBP is the use of sufficient volume of autologous blood. The lower limit may be 15 ml. Injection of blood through the extradural catheter, as opposed to directly through the extradural needle, does not seem to be important for success in prophylaxis. Both Ackerman and Colclough [4] and our group injected autologous blood via the catheter with excellent results.

Our data also suggest that the efficacy of the prophylactic blood patch is consistent over a broad range of intervals between dural puncture and EBP. The prophylactic EBP was effective in all six labour patients, despite the variability in duration of the second stage and the fact that two patients required forceps delivery. The mode of delivery and duration of the second stage of labour did not appear to alter the effectiveness of prophylaxis.

Several investigators have demonstrated that EBP may be performed safely without severe or permanent complications [5]. Opponents of EBP cite formation of abscess and fibrinous arachnoiditis as serious potential complications. However, if a strict aseptic technique is utilized, the incidence of infection should be no higher than that caused by routine lumbar puncture. DeGiovanni, Galbert and Wahle [6] demonstrated microscopically that deliberate placement of non-anticoagulated blood in the extradural space of sheep was associated with no more tissue reaction than routinely performed lumbar punctures.

Three of our 10 patients complained of mild backache at the site of the EBP. All these patients classified this problem as minor and in only one did this persist for as long as 2 weeks. The small possibility of a transient mild backache seems preferable to a 70–80% incidence of post-lumbar puncture cephalalgia. Prophylactic injections of saline reduce the incidence of the cephalalgia, but the efficacy is considerably less than a prophylactic EBP. As hundreds of EBP are performed yearly without reports of serious complications, we prefer the latter method of treatment. In order to substantiate this assertion, we are currently initiating a prospective study in four institutions to compare prophylactic EBP with prophylactic saline injections.

In conclusion, if an extradural catheter has been inserted after an inadvertent dural puncture, it appears that injection of a sufficient quantity of autologous blood is probably both safe and reliable, and may prevent post-lumbar puncture headache.

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PROPOFOL REDUCES SEIZURE DURATION IN PATIENTS HAVING ANAESTHESIA FOR ELECTROCONVULSIVE THERAPY

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SUMMARY

Twenty-five patients received either methohexitone 1.0 mg kg^{-1} or propofol 1.3 mg kg^{-1} to induce anaesthesia during two separate electroconvulsive therapy (ECT) treatments. A forearm was isolated before administration of suxamethonium 0.5 mg kg^{-1}, so that unmodified seizure duration could be measured. Bifrontotemporal electrodes were applied to administer a standard 3-s ECT shock. Median (quartile deviation) duration of seizure was reduced significantly after propofol (19.0 (9.0) s), compared with after methohexitone (33.0 (7.8) s). Therefore propofol may not be an appropriate anaesthetic for ECT because of its adverse effect on seizure duration.

Electroconvulsive therapy (ECT) is an effective treatment for depression [1]. The therapeutic effect depends upon the production of a bilateral, generalized convulsion, and there may be a minimum duration of seizure necessary for successful treatment [2]. It is important to study the effects of anaesthetic techniques on ECT-induced seizures, because the response to ECT may be attenuated if anaesthesia abolishes or inhibits seizures. Patients having ECT require repeated anaesthesia, and propofol would seem to be an ideal drug for this circumstance, as it produces rapid and complete recovery. The present study compared duration of seizure during ECT after anaesthesia with either propofol or methohexitone.

METHODS AND RESULTS

Local Ethics Committee approval was granted for the study, which involved nine male and 16 female depressed patients undergoing a course of bilateral ECT. Patients gave informed consent to take part in the study, and no patient treated under the provisions of the Mental Health Act was included. Each patient acted as their own control, and was studied during two ECT treatments, separated by an interval of at least 1 week. Anaesthesia was induced using either propofol 1.3 mg kg^{-1} or methohexitone 1.0 mg kg^{-1}, given in a random order, over 20 s, and this was followed by suxamethonium 0.5 mg kg^{-1}. The use of any anaesthetic agent shortens the duration of ECT seizure in a dose related manner; thus the smallest effective doses of propofol and methohexitone were selected (approximately 67% of the usual induction doses). Before administration of the neuromuscular blocker, the forearm was isolated, by inflation of a cuff to a pressure exceeding systolic arterial pressure, so that unmodified seizure duration could be measured, using a stopwatch. After induction, the lungs were ventilated with 10 breaths of 100% oxygen using a face mask and oropharyngeal airway. Oxygen saturation was measured using a pulse oximeter (Ohmeda Biox 3700). Bifrontotemporal electrodes were applied in a standard position, and a 3-s shock was administered from an Ectron Duopulse machine set on ECT 2. Recording the duration of seizure is standard practice in our ECT unit, and the duration was timed by a nurse, who was not aware of the purpose of the study. Duration of seizure was analysed using the Mann–Whitney *U* test and linear regression.

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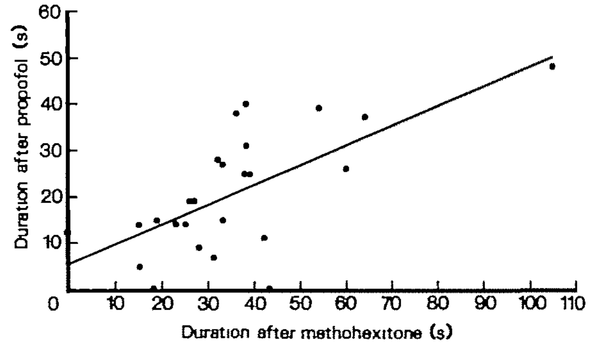

FIG. 1. Duration of seizure after propofol or methohexitone. $y = 0.43x+5.6$, SEM = 9.9, $t = 4.33$; $P < 0.01$.

The mean (SD) ages and weights of the patients were 45.5 (15.8) yr and 75.0 (25.2) kg, respectively. The mean (SD) doses of induction agents were methohexitone 74.5 (26.3) mg and propofol 100.0 (34.3) mg. Transcutaneous oxygen saturation did not decrease to less than 90% during any treatment. The median (quartile deviation) duration of seizure was reduced significantly after propofol: 19.0 (9.0) s, compared with 33.0 (7.8) for methohexitone ($Z = 2.94$, $P < 0.01$). Fourteen patients had seizures of less than 25 s duration after propofol, compared with six patients after methohexitone (Chi square = 4.08, $P < 0.05$). There was a significant positive correlation between seizure duration after methohexitone and after propofol ($t = 4.33$, $P < 0.01$) (fig. 1).

COMMENT

Althesin was not recommended for ECT anaesthesia, as it reduced duration of seizure by more than 50% [3]. The superior anticonvulsant effect of Althesin over methohexitone, at equi-anaesthetic doses, was supported by studies of chemically induced seizures in rats [4]. Although animal work has not indicated that propofol possesses anticonvulsant activity [5], the present study has shown that duration of ECT seizures was reduced significantly by the use of a small dose of propofol. This ability of propofol to reduce electrically induced seizures has important implications and deserves further study.

It has been suggested that a minimum seizure duration of 25 s is desirable during ECT [6]. In the present study, more than twice the number of patients failed to achieve this after propofol than after methohexitone. We observed a positive correlation between duration of seizure after propofol and after methohexitone, and this suggests that patients who had short seizures after methohexitone were more likely to have inadequate seizures after propofol. This adverse effect of propofol on duration of seizure suggests that it may not be an appropriate choice for anaesthesia during ECT, for which methohexitone remains the standard agent.

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EFFECTS OF NADOLOL ON ARRHYTHMIAS DURING LAPAROSCOPY PERFORMED UNDER GENERAL ANAESTHESIA

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SUMMARY

Cardiac arrhythmias are a well recognized complication of anaesthesia for laparoscopy. The effect of nadolol, given by mouth 12 h before operation, was compared with placebo on arrhythmias in 86 females undergoing laparoscopy. All types of arrhythmia were documented; there was a 97% incidence in the placebo group, but in the nadolol group there was a smaller incidence of supraventricular tachycardia, ventricular ectopics and atrioventricular dissociation ($P < 0.01$). There was no significant difference in the incidence of sinus bradycardia. Nadolol may be recommended as a safe agent to be given by mouth before laparoscopy to reduce the frequency of cardiac arrhythmias during anaesthesia.

There is a well recognized incidence of potentially serious cardiac arrhythmias during general anaesthesia for gynaecological laparoscopy [1]. This incidence may reflect the effects of volatile anaesthetic agents, but other precipitating factors include increased sympathoadrenal activity secondary to surgical stimulation of laparoscopy, and reflex increase in cardiac vagal tone, secondary to peritoneal manipulation, which may lead to severe bradycardia, asystole, or both [2].

Previous studies have suggested that prior administration of beta-adrenoreceptor blocking compounds may reduce the frequency of arrhythmias during halothane anaesthesia [3]. The present study examined the effects of pretreatment with nadolol on the incidence of arrhythmias in patients undergoing laparoscopy.

METHODS AND RESULTS

Eighty-six patients (mean age 34.2 yr) gave informed written consent to the study. None had evidence of cardiac disease and none was receiving cardioactive drugs. Twelve hours before laparoscopy, patients were administered either nadolol or placebo tablets by mouth in a double-blind randomization schedule. The first 40 patients were given nadolol 40 mg or placebo, but as profound bradycardia was noted in a few, the dose of nadolol was reduced to 20 mg in the subsequent randomized group. All patients were premedicated with papaveretum 15 mg with hyoscine 0.3 mg i.m. 1 h before anaesthesia.

General anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. and maintained with 66% nitrous oxide and 1–2% halothane in oxygen, followed by suxamethonium 1 mg kg^{-1} i.v. to facilitate tracheal intubation. Subsequently the patients breathed spontaneously.

Laparoscopy was performed in a conventional manner with the patient in a 10° Trendelenburg position and the peritoneal cavity filled with 4 litre of carbon dioxide. The electrocardiogram was continuously monitored and permanent records were made using Holter Monitors. These were subsequently replayed on a Reynolds Pathfinder Display Unit and all new arrhythmic events or conduction defects noted. Each tracing was interpreted by two observers, blinded to the study. The incidence of arrhythmias was compared using Fisher's probability test. As there was no difference between the two treatment groups,

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TABLE I. *Classification of new arrhythmic events or conduction defects during laparoscopy.* *$P < 0.01$; **$P < 0.05$, *compared with placebo*

	Placebo ($n = 47$)	Nadolol 40 mg ($n = 20$)	Nadolol 20 mg ($n = 19$)	Combined nadolol group ($n = 39$)
Sinus bradycardia	22	12	11	23(ns)
Sinus tachycardia	24	4	2	6*
A–V dissociation/ nodal rhythm	14	3	2	5**
Supraventricular				
Ectopics	4	1	0	1(ns)
Tachycardia	2			
Ventricular ectopics	22	0	1	1*

these were combined when compared with placebo. Patient groups were analysed with respect to the distribution of arrhythmic events, as these were often multiple in individual patients.

The placebo group showed a very high incidence of arrhythmias in 97% of patients (table I), including sinus bradycardia (heart rate less than 60 beat min^{-1}) and sinus tachycardia (rate greater than 100 beat min^{-1}). These may have been responses to the procedure or to beta-blockade, but were included as new events in the analysis. Ventricular extrasystoles occurred in 46% of the placebo group, compared with 3% in the treated group ($P < 0.01$). The incidences of sinus tachycardia, atrio-ventricular dissociation and nodal rhythm were less in the treated group ($P < 0.05$). In addition, there were significantly fewer multiple arrhythmic events in the treated group ($P < 0.05$). Sinus bradycardia occurred in similar numbers in both the treated and placebo groups, but was clinically severe enough to require treatment with atropine in only four subjects.

There appeared to be no difference in efficacy between the two doses of nadolol.

COMMENT

This study has confirmed the previously reported high incidence of arrhythmias observed in young healthy patients. Inappropriate sinus tachycardia may reflect sympathoadrenal activity occurring in any surgical procedure, and was seen in 51% of the placebo group. Increased vagal tone, secondary to peritoneal manipulation, may have precipitated the bradycardia noted in both groups. Other factors in laparoscopy include the use of carbon dioxide to fill the peritoneal cavity. Scott and Julian [3] attributed a high incidence of arrhythmias to a degree of hypercapnia produced when carbon dioxide was used, in comparison with nitrous oxide. However, the use of nitrous oxide carries a risk of explosion in these procedures when diathermy is used [4].

Artificial ventilation is known to prevent hypercapnia and hypoxia [5]. However, the results of the Working Party on the confidential enquiry into gynaecological laparoscopy showed that the overall complication rate was higher during controlled ventilation than with spontaneous ventilation (3.8% *v.* 2.7% ($P < 0.01$)) [6].

The high incidence of arrhythmias observed in our study may reflect the definition of arrhythmias which included sinus tachycardia and sinus bradycardia. However, the types of arrhythmia are similar to those reported previously, with a high incidence of ventricular ectopics and nodal rhythm.

Nadolol is a non-selective beta-blocker with no membrane stabilizing or intrinsic sympathomimetic activity and a long half-life. In the present study it was given as a single oral dose 12 h before anaesthesia. This allowed beta-blockade to be sustained for a prolonged period. There were no significant clinical problems produced by nadolol. During anaesthesia four patients in the treatment group had bradycardia which was antagonized easily with atropine. As the incidence of arrhythmias was reduced by pretreatment with both 20 and 40 mg of nadolol, we suggest that the smaller dose of 20 mg should be used.

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EFFECTS OF ISOFLURANE ON INTRAVENTRICULAR PRESSURE IN NEUROSURGICAL PATIENTS

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SUMMARY

The effect of isoflurane on intraventricular pressure (IVP) was examined during nitrous oxide with fentanyl anaesthesia in patients undergoing craniotomy during normocapnia or hypocapnia. Hypocapnic patients ($n = 30$, Pa_{CO_2} 3.3 (0.1) kPa) were allocated to three groups (A, B, C; $n = 10$ each) according to the inspired concentration of isoflurane (1%, 1.5%, 2%). Normocapnic patients ($n = 10$, Pa_{CO_2} 4.7 (0.1) kPa) received an inspired concentration of 1% isoflurane (group D). In patients in groups C and D, IVP increased significantly in response to isoflurane ($P < 0.01$). In groups A and B, IVP did not change significantly ($P > 0.05$). Mean arterial pressure and cerebral perfusion pressure decreased significantly ($P < 0.001$) in all groups in response to isoflurane.

The use of isoflurane is controversial in patients with intracranial lesions before opening of the dura. Some human studies have shown that 1% isoflurane caused no significant change in intracranial pressure (ICP) [1–3], but others have demonstrated that significant increases in ICP may occur during both normocapnia [4] and hypocapnia [5]. At deeper levels of isoflurane anaesthesia (1.5% and 2% concentrations) ICP increases in most patients with intracranial disorders [1–3].

The purpose of the present study was to evaluate the effect of 1%, 1.5% and 2% isoflurane on intraventricular pressure (IVP) in a group of patients with intracranial disorders in whom hypocapnia was induced before the introduction of isoflurane. We have also investigated the effect of 1% isoflurane on IVP in normocapnic patients.

METHODS AND RESULTS

Informed consent of all patients was obtained for the study, which was approved by our Institution's Human Research Committee. We studied 40 adult patients undergoing craniotomy for intracranial neoplasm ($n = 31$), intracranial ruptured vascular malformation ($n = 7$) and intracerebral haemorrhage ($n = 2$).

Patients were premedicated with atropine 0.01 mg kg^{-1}, fentanyl 0.5 mg i.v. and droperidol 5 mg i.v. General anaesthesia was induced with thiopentone 6 mg kg^{-1}, and maintained with 66% nitrous oxide in oxygen and intermittent supplementary doses of fentanyl. Vecuronium 0.2 mg kg^{-1} was administered to facilitate tracheal intubation. A continuous infusion of vecuronium was administered to provide neuromuscular blockade. Minute ventilation was controlled with a Kontron ABT 4100 ventilator and adjusted to maintain hypocapnia (an end-tidal carbon dioxide partial pressure ($P\text{E}'_{CO_2}$) of 3.04 kPa) or normocapnia ($P\text{E}'_{CO_2}$ 4.3 kPa) displayed on a Hewlett–Packard capnometer Mod. 47210A. The lateral ventricle and radial artery were cannulated. The transducers were positioned at the level of the external auditory meatus. All pressures are expressed as the electronically integrated means. Cerebral perfusion pressure (CPP) was calculated as mean arterial pressure (MAP) minus mean IVP (MIVP). Arterial pressure (AP) and IVP were recorded on a two-channel Hewlett–Packard recorder Mod. 78172A.

When stable values for IVP were reached, after

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TABLE I. *Mean (SEM) intraventricular pressure (MIVP), mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) values before (control) and after (final) isoflurane administration. Significantly different from control values*: *$P < 0.01$; **$P < 0.001$

Group	n	Pa_{CO_2} (kPa)	MIVP (mm Hg)		MAP (mm Hg)		CPP (mm Hg)	
			Control	Final	Control	Final	Control	Final
A	10	3.44 (0.17)	12.9 (2.1)	12.4 (2.1)	106 (5.3)	83.7 (3.8)**	93.4 (6.6)	71.3 (5.0)**
B	10	3.21 (0.13)	7.5 (1.1)	7.8 (0.6)	101 (3.4)	70.8 (3.2)**	93.7 (3.5)	63.0 (3.2)**
C	10	3.39 (0.17)	13.0 (2.5)	15.8 (2.9)*	111 (6.5)	69.9 (3.6)**	98.1 (6.6)	54.1 (2.9)**
D	10	4.75 (0.12)	14.1 (2.3)	19.4 (3.6)*	93 (4.6)	78.0 (4.4)**	79.1 (5.3)	58.6 (4.4)**

5–10 min (control values), 1%, 1.5% or 2% isoflurane was administered to hypocapnic patients (groups A, B, C, respectively) and 1% isoflurane to normocapnic patients (group D). AP and IVP were recorded for 10 min after administration of isoflurane and before surgery was continued. In two patients in group C and one in group D, cerebrospinal fluid (CSF) drainage or hyperventilation was established before the end of the study because the cerebral perfusion pressure (CPP) decreased to less than 50 mm Hg (the lowest limit permitted by our Human Research Committee). CSF drainage in the group C patients and hyperventilation in the group D patient rapidly increased the CPP.

The patients were supine with a 20° head-up tilt and 10° thorax-up tilt. Diuretics and hyperosmotic agents were not administered. Arterial blood samples were taken for the measurement of blood-gas values 5 min before isoflurane was administered. The time interval between induction of hypocapnia and administration of isoflurane was approximately 30 min.

All data are expressed as mean (SEM). Sequential values for IVP and AP between control-final were subjected to Student's t test for paired data. A value of $P < 0.05$ was regarded as significant.

In group A, IVP did not change significantly (table I). In five of 10 patients who had intracranial pressure control values greater than 15 mm Hg, ICP was minimally affected (from 18.4 (1.5) to 18.2 (1.5) mm Hg) during administration of 1% isoflurane. In contrast to the findings obtained in group A, where there were essentially no changes in IVP during 1% isoflurane, nine of 10 patients in group D developed an increase in IVP ($P < 0.01$) during administration of 1% isoflurane. Furthermore, in two of the patients in group D who had increased control IVP values (23–27 mm Hg), the addition of isoflurane increased IVP to 35–43 mm Hg. These increases were corrected rapidly by hyperventilation.

In group B, IVP did not change significantly. In this group control values were lower than in the other groups. However, the addition of 1.5% isoflurane did not change IVP in three patients with greater control values (12 mm Hg).

In group C, IVP increased significantly ($P < 0.01$).

MAP and CPP decreased significantly ($P < 0.001$) in all groups. The decrease was greater in hypocapnic patients when the inspired isoflurane concentration was increased to 1.5% and 2%.

COMMENT

In our study, 1% isoflurane caused the greatest changes in ICP in the normocapnic patients. Similar results have been reported by Adams and colleagues [4], but they contrast with those of Mazzarella and colleagues [2] and Campkin [1], who found that ICP did not change significantly in response to 1% isoflurane. In addition, Campkin found that 1% isoflurane administration decreased ICP in the only two patients who had clinical evidence of increased ICP. From this observation the author concluded that isoflurane "appears to be a suitable agent even when intracranial hypertension is present" [1]. In our study the greatest increases in ICP (16–12 mm Hg) occurred in patients with the highest control ICP (27–23 mm Hg) and we feel that the opposite conclusion may be drawn from our data. Therefore, we believe that isoflurane should not be used for induction of anaesthesia in spontaneously breathing neurosurgical patients and in normocapnic patients before opening of the dura.

Hypocapnia before administration of 1% isoflurane was effective in preventing increases in ICP, even in five of 10 patients who had control values greater than 15 mm Hg. This observation contrasts with that of Grosslight and colleagues [5], who reported that induction of hypocapnia was ineffective in preventing increases in ICP in patients with lateral shift of midline structures. However, our study differs in that fentanyl was used for analgesia and ICP was assessed in the absence of surgical interference.

Hypocapnia before administration of 1.5% isoflurane was also effective in preventing increases in ICP. It should be noted that the control values of ICP were lower than those found in the other groups. This observation was unexpected because there were no clinical signs or symptoms to suggest this. Similar results in patients with intracranial pressures less than 15 mm Hg have been reported [2].

At deeper levels of isoflurane anaesthesia (2% concentration), hypocapnia was not adequate to prevent increases in ICP. In addition administration of 2% isoflurane produced striking reductions in CPP, suggesting that this should not be used to produce rapidly deeper anaesthesia when the skull is closed. In a recent study by Lundar and colleagues [3], IVP increased significantly during 2% isoflurane in hydrocephalic patients.

In all groups, isoflurane reduced arterial pressure in a dose dependent fashion. The decreases in CPP in groups C and D were greater than the reductions in AP, as IVP increased.

In conclusion, our results confirm the principle that, in neuroanaesthesia, hyperventilation should be established before volatile agents are administered and that 1% and 1.5% isoflurane may be used safely before opening of the dura in the presence of hypocapnia. However, at deeper levels of isoflurane anaesthesia (1.5% concentration), CPP approaches the ischaemic threshold, indicating that it should be used with caution in situations where cerebral autoregulation may be impaired. Administration of 1% and 2% isoflurane should be avoided during normocapnia and hypocapnia, respectively, before opening of the dura.

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ANAESTHETIC MANAGEMENT OF CAESAREAN SECTION FOR A MOTHER WITH PRE-ECLAMPSIA, THE KLIPPEL-FEIL SYNDROME AND CONGENITAL HYDROCEPHALUS

A. M. BURNS, P. DORJE, E. G. LAWES AND M. S. NIELSEN

SUMMARY

A mother with the Klippel-Feil syndrome, congenital hydrocephalus and increased intracranial pressure presented for delivery by Caesarean section at 33 weeks because of pre-eclampsia. Anaesthetic management comprised awake intubation using the fibreoptic bronchoscope, followed by induction and maintenance of general anaesthesia for the delivery of a live male infant. This case report describes the problems arising under these circumstances and the relative merits of different anaesthetic techniques.

The anaesthetic management of a patient undergoing Caesarean section is known to present a challenge, with particular difficulties relating to tracheal intubation and the dangers of the acid aspiration syndrome. We report the case of a mother with Klippel-Feil syndrome and congenital hydrocephalus complicated by epilepsy and increased intracranial pressure, requiring delivery by Caesarean section at 33 weeks gestation because of pre-eclampsia.

CASE REPORT

A 27-yr-old primiparous housewife presented with pre-eclampsia at 30 weeks gestation. Although found to be abnormal at birth she had been lost to follow-up until she presented at age 23 yr with epileptiform fits. Investigation at that time demonstrated chronic hydrocephalus with aqueduct stenosis and hindbrain abnormality. The fits were thought to have occurred secondary to an episode of acute-on-chronic increased intracranial pressure and were controlled well with carbamazepine. Ventriculo–peritoneal shunting was thought not to be indicated because of the risks of sudden neurological deterioration and the possibility of developing subdural haematoma. In addition, she had obvious clinical and radiological features of the Klippel-Feil syndrome (figs 1, 2), in which fusion of a variable number of cervical vertebrae results in restriction of neck movement and a short neck. More extensive fusions are associated with abnormalities of other systems, including the cardiovascular, respiratory, genitourinary and musculoskeletal systems [1].

On admission the patient had marked peripheral oedema, arterial pressure of 160/100 mm Hg and associated proteinuria. There were no signs of decompensation of her hydrocephalus or of impending eclampsia. Therapy commenced with methyl dopa 250 mg 6-hourly when arterial pressure remained consistently increased, with systolic pressures between 140 and 165 mm Hg and diastolic pressures between 90 and 105 mm Hg. The degree of proteinuria increased during her admission, from 5.9 g litre^{-1} to 11.7 g litre^{-1}. Other biochemical indices of renal function and the platelet count remained within the normal range. Immediately before operation, urea was 5.7 mmol litre^{-1}, creatinine 85 μmol litre^{-1}, haemoglobin 13 g dl^{-1} and platelet count 210 × 10^9 litre^{-1}.

Further examination revealed an obese lady with a large cranium and the obvious abnormalities of the Klippel-Feil syndrome. There was limited neck extension, to approximately 30°, and

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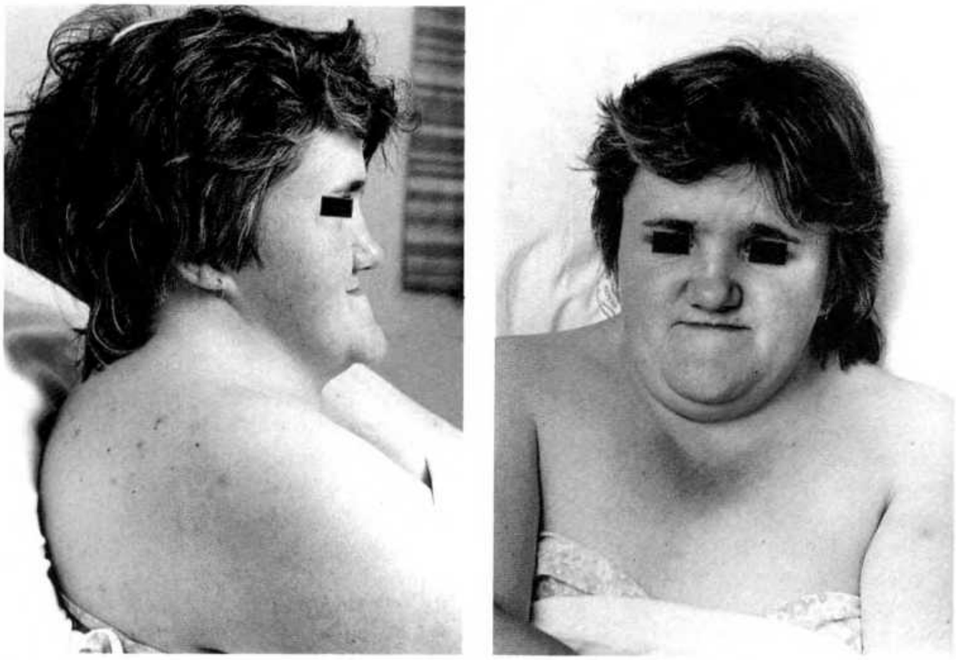

FIG. 1. Antero–posterior and lateral views of patient to demonstrate clinical features of Klippel-Feil Syndrome and large cranium secondary to congenital hydrocephalus.

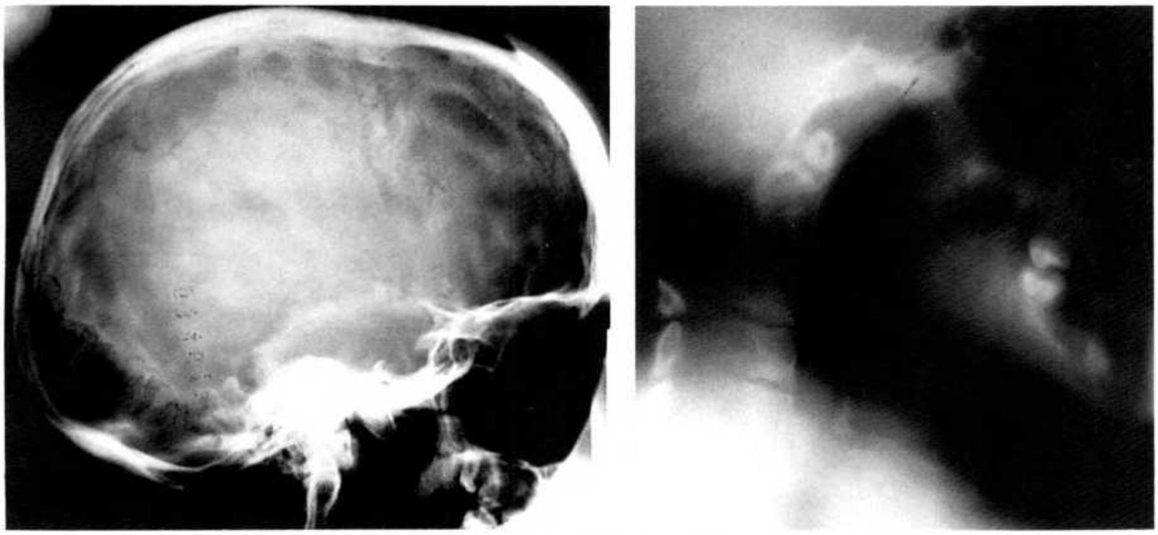

FIG. 2. Lateral radiological view of cranium demonstrating features of chronic hydrocephalus, and lateral tomogram of cervical spine in full extension to demonstrate fusion of several cervical segments and abnormal morphology (note proximity of mandible to chest).

the atlanto–occipital joint was known to be fused. She had a small maxilla and large mandible, and was unable to open her mouth beyond two finger widths. The soft palate was not visible on mouth opening. Although she appeared dyspnoeic at rest, she gave no history of reduced exercise tolerance, and on examination there was no cardiovascular or respiratory abnormality. It was considered that the apparent dyspnoea was consistent with pregnancy, obesity and cigarette consumption of 20 day^{-1}; formal pulmonary function tests were not performed.

The decision was taken by the obstetricians and neurologists that delivery by Caesarean section was the preferred method, in order to avoid increases in intracranial pressure associated with labour. Under the circumstances, it was considered that the safest anaesthetic technique comprised awake intubation using the fibreoptic bronchoscope, proceeding to general anaesthesia. Caesarean section was planned at 33 weeks gestation, after 5 days monitoring when evidence of fetal distress appeared on the cardiotochograph.

In anticipation of the possibility of an emergency operation, the patient received ranitidine as antacid prophylaxis for 5 days before the procedure. In view of the nature of the planned procedure, premedication of temazepam 10 mg and metoclopramide 10 mg was given. On arrival in the anaesthetic room, the patient was given 30 ml of sodium citrate 0.3 mol litre^{-1} and ECG and automatic arterial pressure monitoring commenced. Arterial pressure was measured at 2-min intervals during tracheal intubation and the subsequent anaesthetic and remained within acceptable limits. The highest recorded systolic pressure was 180 mm Hg and the highest diastolic pressure 105 mm Hg (fig. 3). The fetus was monitored intermittently using a sonicaid. A left lateral tilt was maintained throughout the procedure. Sedation was provided to facilitate insertion of the bronchoscope using increments of midazolam (total 10 mg) and droperidol 5 mg given after 25 min of attempting intubation. Before intubation, the nasal mucosa was sprayed with cocaine, and the pharynx and larynx with 10 % lignocaine 1 ml via the bronchoscope. Awake nasal intubation was achieved using the fibreoptic bronchoscope after 55 min. Although the cords were visualized easily through the bronchoscope, considerable difficulty was experienced in advancing the tracheal tube over the bronchoscope and into the larynx. This is thought to result from the tip of the tracheal tube catching on the epiglottis or the arytenoid cartilage, and various modifications of the technique have been described to overcome the problem [2]. Subsequently, general anaesthesia was induced with thiopentone and maintained with oxygen, nitrous oxide and enflurane, with an increment of fentanyl being given after delivery of a live male infant. Muscle paralysis was obtained using vecuronium.

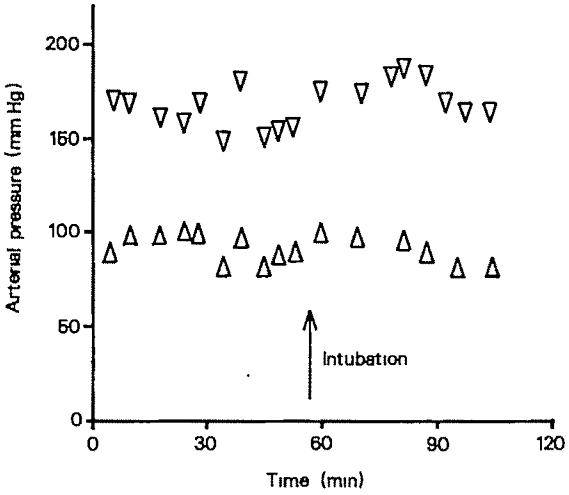

FIG. 3. Record of arterial pressure during intubation and anaesthesia. ▽ = Systolic pressure; △ = diastolic pressure.

It was noted that direct laryngoscopy after induction revealed an easily visualized larynx! The right kidney was found to be absent at laparotomy.

At the end of the procedure residual neuromuscular block was antagonized with neostigmine and atropine, and the trachea was extubated with the patient in the left lateral position as she awoke. No airway difficulties were encountered during the recovery period.

The patient made an uneventful recovery, with signs of her pre-eclampsia rapidly resolving. There was no recall of the intubation subsequent to spraying of the nasal mucosa and no evidence of awareness after induction. The baby required a short period of artificial ventilation after delivery because of poor respiratory effort, but subsequently made excellent progress. There was no evidence that he had inherited the Klippel-Feil syndrome.

DISCUSSION

The anaesthetic management of this patient was based on the following aims. First, in view of the predicted difficulty with tracheal intubation, it was considered essential that the airway was secure before induction of general anaesthesia. Second, large increases in arterial and intracranial pressure should be avoided. Third, the chosen technique should minimize the known risks of obstetric anaesthesia.

Intubation of the trachea of a patient with Klippel-Feil syndrome has not been described, although Mather described a case of impossible direct laryngoscopy because of limited neck extension in achondroplasia [3]. In view of the clinical findings, it could be predicted that our patient was likely to present difficulty with intubation [4] and therefore a rapid sequence induction was inappropriate, as would have been a gaseous induction in the presence of the risk of aspiration.

The choice of anaesthetic technique lay between general or regional anaesthesia. A general anaesthetic offered the advantages of maintaining cardiovascular stability and controlling arterial carbon dioxide tension, thus maintaining cerebral perfusion whilst avoiding cerebral vasodilatation and an increase in intracranial pressure. However, it is well recognized that there is a marked hypertensive response to tracheal intubation and extubation, and that this is exaggerated in the hypertensive patient [5]. In the patient with pre-eclampsia this may be severe enough to precipitate pulmonary oedema and intracerebral oedema and haemorrhage [6, 7]. A variety of techniques has been used to attenuate this response [8–10].

In the patient with known increased intracranial pressure, the hypertension coincident with intubation may be sufficient to abolish cerebral autoregulation and precipitate a large increase in intracranial pressure secondary to oedema formation [11], with neurological deterioration and possible tentorial herniation. Epilepsy may also be precipitated.

In view of these considerations, some may regard regional anaesthesia as the most appropriate technique. The cerebrospinal fluid pressure in normal labouring mothers is normal at rest, but increases during contractions to a value approaching 7 kPa in the second stage of labour [12, 13]. The majority of this increase results from skeletal muscle contraction secondary to pain, and can therefore be modified by the use of general or regional anaesthesia. There have been two case reports which described the management of labour by regional anaesthesia in patients with grossly increased intracranial pressure secondary to malignant disease [14, 15]. It was found that effective uterine contractions in one produced an increase in intracranial pressure which was sufficient to result in alteration of conscious level [14]. Under these circumstances it was felt inappropriate to allow our patient to undergo vaginal delivery.

Extradural anaesthesia for Caesarean section was considered when the patient first presented. In the absence of contraindications, regional anaesthesia is now considered to be an integral part of the management of the pre-eclamptic patient [16]. However, whilst the incidence of dural puncture is very low in experienced hands, it was considered to be unacceptable in this instance because of the possibility of lethal neurological deterioration. In addition, recent work has suggested that the volume of local anaesthetic agent required may increase intracranial pressure [17].

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ADENOTONSILLAR HYPERTROPHY AND COR PULMONALE

D. W. YATES

SUMMARY

Pulmonary hypertension is a known complication of chronic upper airway obstruction resulting from adenotonsillar hypertrophy. Surgical removal of the hypertrophic tissue usually leads to rapid improvement. Although anaesthetic management is potentially hazardous, little has been written on this aspect. Six paediatric patients (all male) are reported here, and a suitable anaesthetic technique is described.

Pulmonary heart disease occurring in children with chronic upper airway obstruction resulting from adenotonsillar hypertrophy, was first reported in 1965 [1], and has since been reported from this and from other causes of airway obstruction, such as the Pierre-Robin anomaly [2], post-intubation stenosis [3] and Down's syndrome [4]. When adenotonsillar hypertrophy is the cause, surgical removal of the hypertrophic tissue generally leads to rapid improvement in the clinical state, although the electrocardiographic changes may take some months to revert to normal [5].

Despite the implicit problems for the anaesthetist, and a death under anaesthesia reported by Wilkinson and colleagues [6], very little has appeared in the literature concerning the anaesthetic management of such patients.

CASE REPORTS

Over a 9-month period, 26 children aged less than 5 yr presented for removal of tonsils, adenoids or both, at Harare Central Hospital. A history of airway obstruction, mouth breathing, snoring or sleep apnoea was present in 15. Electrocardiograms (ECG) and chest x-rays were performed on these 15; nine were normal. The six children reported below showed signs of cor pulmonale. Electrocardiographic criteria for diagnosis were those laid down in a standard paediatric text book, and included the presence of large p-waves in leads II and V1, large R-waves in V1, and deep S-waves in V6 [7]. Echocardiography was carried out on two patients.

Once the primary diagnosis of upper airway obstruction had been made and any heart failure or pneumonia treated, operation was performed as soon as possible. This consisted initially of an examination under anaesthesia, followed in all cases by adenoidectomy, with additional tonsillectomy in some.

No premedication was given, and an inhalation induction was performed with halothane in oxygen (four patients), or halothane and nitrous oxide in oxygen (two patients). In all patients except No. 1 the trachea was intubated while the patients were breathing spontaneously once an adequate depth of anaesthesia had been attained. After intubation, anaesthesia was continued with spontaneous or assisted respiration using a T-piece breathing system with halothane and nitrous oxide in 50% oxygen. Monitoring was by ECG and precordial stethoscope in all patients. No analgesia was given before operation, and non-opioid analgesics were prescribed in the post-operative period.

Potentially serious problems were encountered in patient No. 1, who inadvertently received sedative premedication, and in whom anaesthesia was induced with nitrous oxide and halothane in oxygen.

Patient No. 1

A boy aged 14 months presented to the paediatricians with pneumonia and congestive

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cardiac failure, and upper airway obstruction. The ECG showed signs of right ventricular hypertrophy, with right axis deviation of 160°, tall R-wave in lead V1 and deep S-wave in lead V6, and borderline p-pulmonale in leads II and V1. He was initially treated with digoxin, frusemide and erythromycin, and referred to the ENT department for surgery.

Premedication with diazepam by mouth was given in error. Inhalation induction performed with halothane and nitrous oxide in 50% oxygen was "stormy", with breath-holding, coughing and cyanosis, and the trachea was intubated after the administration of suxamethonium. No adverse cardiovascular changes (hypotension or bradycardia requiring treatment) occurred.

Adenotonsillectomy was performed with some improvement in his breathing, although mild stridor persisted, probably epiglottic in origin. He had no further episodes of cardiac failure or pneumonia over the following 3 months.

Patient No. 2

A boy aged 8 months presented to the paediatricians with a history of dyspnoea since birth. He was found to be in congestive cardiac failure, which was treated with digoxin and frusemide. He was slow to respond to treatment, and after 3 weeks he was referred to the ENT surgeons, as it was suspected that upper airway obstruction was the primary problem.

Before surgery the ECG showed right axis deviation, and increased heart size was seen on chest x-ray. A marked respiratory acidosis was present when the child breathed 40% oxygen (pH 6.88, $P\mathrm{co}_2$ 9.04 kPa, $P\mathrm{o}_2$ 14.9 kPa in arterial blood). No premedication was given.

On the patient's arrival in theatre a relative bradycardia of 80 beat min^{-1} was noted, which was treated with atropine. Inhalation induction using halothane in oxygen was uneventful, and adenoidectomy was performed. His breathing improved immediately after operation, and he had no further episodes of heart failure.

Patient No. 3

A boy aged 18 months with congestive cardiac failure and obviously obstructed breathing was admitted by the paediatricians. He was treated medically with digoxin and frusemide. Chest x-ray showed cardiomegaly, which was demonstrated on echocardiography to be the result of moderate dilatation of the right ventricle. After initial medical treatment the arterial $P\mathrm{co}_2$ was mildly increased, at 6.09 kPa. He was referred for surgery.

No premedication was given, and inhalation induction was performed using halothane in oxygen. Maintenance of a clear airway was difficult, and the best position was eventually obtained with a pillow under the back, and with full neck and head extension. Continuous positive airway pressure (CPAP) was very helpful and no cyanosis or cardiovascular changes were observed. Adenoidectomy was performed with rapid resolution of his respiratory problems.

Patient No. 4

A boy of 4 yr was admitted by the paediatricians, with congestive cardiac failure and pneumonia, which was treated with digoxin, frusemide and erythromycin. ECG showed right axis deviation to 160°, deep S-waves in lead V6, and p-pulmonale in leads II and V1 (fig. 1). Chest x-ray

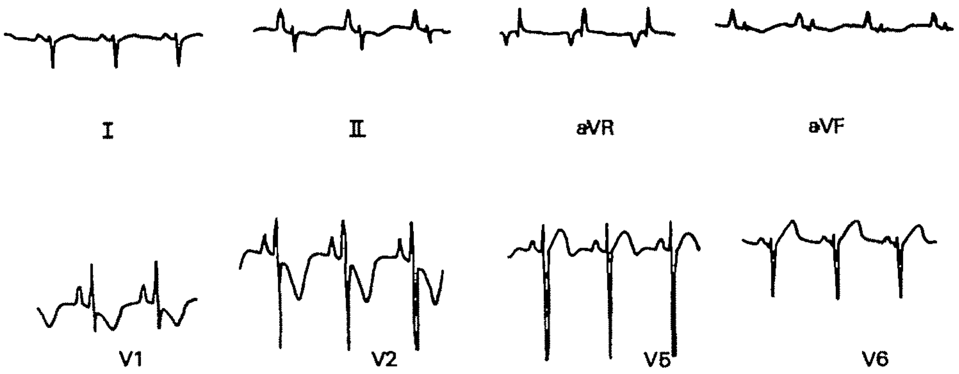

FIG. 1. Preoperative ECG of patient No. 4.

TABLE I. *Patients of 4 yr and younger presenting for adenotonsillectomy.* *$P < 0.01$ (χ^2 *test*)

	Admitted	No respiratory symptoms	With respiratory symptoms	Cor pulmonale
Male	20*	6	14	6
Female	6	5	1	0
Total	26	11	15	6

TABLE II. *Presenting diagnoses and investigations. CCF = Congestive cardiac failure; UAO = upper airway obstruction; RAD = right axis deviation; RVH = right ventricular hypertrophy.* **ECG technically unsatisfactory. Echocardiography showed right ventricular dilatation*

Patient No.	Age	Sex	Presentation	Chest x-ray	ECG
1	14 months	M	CCF/UAO pneumonia	Cardiomegaly B-pneumonia	RAD, RVH p-pulmonale
2	8 months	M	CCF	Cardiomegaly	RAD
3	18 months	M	CCF/UAO	Cardiomegaly	*
4	4 yr	M	CCF pneumonia	Cardiomegaly B-pneumonia	RAD, RVH p-pulmonale
5	3 yr	M	UAO	Cardiomegaly	p-pulmonale
6	15 months	M	CCF Pneumonia	Cardiomegaly B-pneumonia	RAD p-pulmonale

showed cardiomegaly and evidence of bronchopneumonia. The arterial $P\text{CO}_2$ ranged between 6.70 and 9.87 kPa over the following 4 days. Upper airway obstruction was diagnosed, and he was referred to the ENT surgeons.

No premedication was given, and anaesthesia was induced using halothane in oxygen. At laryngoscopy pus and blood were seen in the pharynx, and the larynx was oedematous. Adenotonsillectomy was performed, and a nasotracheal tube left *in situ* for the first 2 days after operation, to allow the oedema to settle.

Histological examination of a biopsy from the posterior pharyngeal wall demonstrated the presence of a tuberculous granuloma, while the tonsils and adenoids showed reactive hyperplasia. Initially, there was little improvement in the airway, although there were no further signs of heart failure. After 1 month of treatment with steroids and anti-tuberculous therapy, only mild stridor was present.

Patient No. 5

A boy aged 3 yr 8 months presented to the ENT surgeons with a 10-month history of airway obstruction, feeding difficulty and noisy breathing. On examination he was mouth-breathing and had clinical cardiomegaly with a prominent parasternal heave. Chest x-ray showed borderline cardiomegaly, and large p-waves were seen in lead II of the ECG.

No premedication was given, and inhalation induction with halothane in oxygen was uneventful. Adenotonsillectomy was carried out, with complete relief of symptoms.

Patient No. 6

A boy aged 15 months admitted by the paediatricians had congestive cardiac failure, which was treated with digoxin and frusemide. The chest x-ray showed increased heart size with pulmonary consolidation, and p-pulmonale and right axis deviation were present on the ECG. The right ventricle was found to be grossly dilated on echocardiography. Upper airway obstruction was noted, and he was referred to the ENT department for surgery.

No premedication was given, and induction of anaesthesia with halothane and nitrous oxide in 50% oxygen was uncomplicated. Large tonsils and adenoids were removed and the post-nasal space was noted to be small. After his operation the child showed slow but steady improvement in his breathing, with no further episodes of heart failure in the 8 months after operation.

Presenting diagnoses and results of the initial investigations are shown in table I. It will be noted that all six of the affected children reported here were boys, as were 20 of the 26 admissions (table II) ($P < 0.01$).

DISCUSSION

Cor pulmonale secondary to upper airway obstruction by adenotonsillar hypertrophy in children is thought to occur as a result of hypoxic pulmonary vasoconstriction during periods of apnoea, which may occur many times at night. With repeated episodes, the increase in pulmonary vascular resistance may become chronic, with resultant dilatation and hypertrophy of the right side of the heart [8], and the eventual development of congestive cardiac failure. Studies on children living at very high altitude have shown that pulmonary hypertension in response to hypoxia is most marked before the age of 5 yr, when right heart and pulmonary pressures, and vascular histology, remain similar to those seen in normal neonates [9].

Children with severe disease from this cause most often present to the paediatric physicians in acute heart failure, as did five of the six patients reported here. In such patients the underlying cause may not be immediately apparent, and conditions such as cardiomyopathy first considered [5]. Exploratory cardiac surgery has been performed [10]. Once airway obstruction has been correctly diagnosed operation becomes an urgent matter, for the existence of a potentially lethal heart condition in these patients is unquestioned.

There is evidence that apparently healthy patients may have unsuspected cor pulmonale, and Wilkinson and colleagues [6] reported a 3% incidence of electrocardiographic signs of right heart strain among 92 children without obvious heart disease, who presented for "routine" adenotonsillectomy. All the affected patients had symptoms of sleep disturbance with apnoea, snoring and daytime somnolence, as did the one such child in this report.

It is important that the pathophysiological process be understood when dealing with such patients, and that possible adverse drug effects on the heart and pulmonary circulation are taken into account. Pulmonary vascular resistance is increased by hypoxia and acidosis [11], and pre- and postoperative sedation, which may lead to further episodes of apnoea, should be avoided [12]. The administration of oxygen in the presence of pulmonary hypertension may lead to either an increase or a decrease in pulmonary artery pressure. In general, vascular resistance seems to be reduced, but respiration may be seriously depressed as a result of loss of hypoxic respiratory drive [1,13]. This probably occurred before operation in patient No. 2.

Nitrous oxide has been shown to increase pulmonary vascular resistance markedly in children with increased pulmonary blood flow, which may have a serious clinical effect [14,15]. It is possible that this also applies to children with increased pressures and normal flow, such as those in this study.

Bjertnaes [16] obtained results in fit young adults which suggested that hypoxic pulmonary vasoconstriction is reduced by halothane and ether, but not by i.v. anaesthetic agents. While this property of halothane may be beneficial, its depressant effects on the heart are obviously undesirable. Although a significant amount of myocardial depression might be anticipated in attaining a sufficient depth of anaesthesia to permit intubation under halothane–oxygen, this did not appear to be a problem in the patients reported here.

If inotropes are required, isoprenaline and dobutamine are probably the most suitable agents, as both have been shown to decrease pulmonary vascular resistance [17].

The technique for anaesthesia found satisfactory by the author includes avoidance of sedative premedication, induction with halothane in oxygen, and intubation without neuromuscular blockade once a sufficient depth of anaesthesia has been attained. It is useful to spray the mouth and pharynx with lignocaine before induction, to facilitate early insertion of an oropharyngeal airway, but care should be taken not to obtund the laryngeal reflexes. Continuous positive airway pressure, easily produced with the Jackson–Rees modification of the Ayre's T-piece, may be very helpful, sometimes having a dramatically beneficial effect on airway management. In the awake patient the prone position often provides the clearest airway [13] and unorthodox positions may be useful during the induction of anaesthesia, as was found in patient No. 3.

Adenotonsillar hypertrophy in these patients is often surprisingly moderate [18], and intubation is not usually a problem. Some authorities have, therefore, recommended that induction should be exclusively by the i.v. route, avoiding the potential problems of a lengthy induction in a patient with a compromised airway. However, difficult intubations have been reported [13], and in two of the patients reported here other pharyngeal pathology was present.

In conclusion, while cases as extreme as those reported here are unlikely to be encountered, signs of cor pulmonale were found in 3% of patients presenting for elective adenotonsillectomy in a British study [6]. The diagnosis should particularly be suspected in children who have a history of sleep apnoea, cyanotic attacks or daytime somnolence. It is recommended that such children be appropriately investigated and managed.

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RECENT ADVANCES IN THERAPY FOR HYPERTENSION

A. M. HEAGERTY

It is axiomatic that man requires an adequate arterial pressure to maintain tissue perfusion. However, diseases of the circulation are observed more frequently in subjects at the upper end of what is a normal distribution of pressures: thus the association between hypertension and cardiovascular morbidity and mortality is real [1]. Indeed, available data suggest that there is a linear increase in mortality with increasing systolic and diastolic pressures above 110/70 mm Hg. Whilst it has been known for some time that treatment of the most severe hypertension prolongs life, it is only comparatively recently that the results have appeared of offering treatment to patients with milder degrees of the disease [2]. The data have pleased and disappointed: decreasing diastolic arterial pressures in the range 90–115 mm Hg has produced a clear reduction in cerebrovascular accidents, but had virtually no impact upon myocardial infarction, and yet coronary events are the commonest complication of mild hypertension. In addition, perhaps predictably, greater benefit accrued from treating patients with sustained diastolic arterial pressures of 100 mm Hg or greater. Even at this arbitrary point in the arterial pressure distribution curve, the economic consequences of treating every adult defined thus would be alarming, assuming that all such individuals were detected; such financial implications become unthinkable if the cut-off point is reset at 90 mm Hg, with an estimated 25 % of the adult population of the U.K. then falling into the potential group needing therapy. At this level, the benefit to an individual is small and possibly outweighed by risks of taking pharmacological agents.

The purpose of this article is to describe current treatment policy regarding hypertension, using pharmacological and non-pharmacological interventions. Newer developments are mentioned also, in line with possible changes which may further modify our thinking.

When to treat hypertension

Whilst there is no doubt that the large multicentre studies were required to examine if treatment is beneficial in severe hypertension, in their execution large populations were exposed to prolonged drug therapy. However, in respect of the Medical Research Council Trial performed in an asymptomatic population [2], one stroke could be avoided in 850 patient years of treatment. Moreover, during the 5 years of study some 15 % of patients had to discontinue bendrofluazide (10 mg daily) or propranolol because of side-effects. Clearly the *individual* benefits of prolonged treatment may be outweighed by the potential problems of taking such drugs. One solution to this would be to try to identify hypertensive patients at greatest risk; for example the elderly are demonstrated to be one such group but, beyond this, asymptomatic patients are difficult to classify in terms of risk. However, stratification of the data from the M.R.C. study showed that there was a sharp increase in vascular events (both cardiac and cerebral) when the diastolic pressure exceeded 100 mm Hg. Therefore, current opinion suggests that patients presenting with mild uncomplicated hypertension should have their arterial pressure reviewed over a period of 6 months. If the diastolic pressure remains consistently greater than 100 mm Hg, drug therapy should be commenced [3]. For those patients with diastolic pressures between 90 and 99 mm Hg, a longer period of observation can be used, accompanied by advice on non-pharmacological means of decreasing arterial pressure. Smoking should be discouraged in both groups of patients, for whilst habitual smoking is not a pressor stimulus *per se*, there is little doubt that smoking and hypertension accelerate atherosclerosis and, therefore, this is a potential lethal combination.

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Non-pharmacological approaches to the control of hypertension

There is now a wealth of information indicating that diet, lack of exercise and alcohol consumption may greatly influence arterial pressure in the community. Data suggest that exercise programmes may decrease arterial pressure independent of any accompanying weight loss; moderate to heavy alcohol ingestion is a powerful pressor stimulus. Both these variables are susceptible to change and, increasingly, physicians are advising their patients on how to achieve this. The dietary issue is more complex and has led to passionate debates in recent years. There is no doubt that there is a close association between hypertension and obesity. It is seen both in primitive and "Westernized" societies, and the Framingham study has demonstrated that relative body weight, weight change with time and skinfold thickness are directly related to arterial pressure and to the ultimate development of hypertension. A variety of mechanisms has been postulated to explain the relationship, notably expansion of blood volume, increased cardiac output, increased sympathetic nervous system activity in obesity, and an associated increase in sodium intake consequent upon the excess calories ingested. The situation remains unresolved. What is clear is that all randomized controlled trials of weight reduction except one have shown a reduction in arterial pressure [4]. Again, the mechanism by which this is achieved is still uncertain; it is possible that it is a result of reduced salt intake, or changes in the fat content of the diet. However, despite the high rate of recidivism that is to be anticipated with this manoeuvre, the motivated patient stands to gain substantially by paying attention to his weight.

The sodium controversy has aroused passions around the world. The debate continues over whether or not an excessive dietary salt intake contributes to the genesis of essential hypertension; on balance the evidence seems to lack credibility [5]. Indeed the Intersalt study has reported recently on the salt intake of 55 populations and found little association between sodium and arterial pressure. On the other hand, it does appear that moderate restriction of sodium intake to 70–80 mmol day^{-1} is beneficial in the established phase of the disease and may obviate the need for drug therapy [4, 5]. However, there is no evidence that restricting the salt intake of the normotensive individual prevents the subsequent development of hypertension. The data on potassium supplementation are not convincing [6], and dietary guidelines directed at increasing this element to reduce arterial pressure would be premature. Similarly, despite sometimes bitter public argument, the case for dietary calcium supplementation being beneficial has slipped into disfavour with the publication of three well-conducted negative trials.

Perhaps the most interesting dietary manoeuvres, which appear to warrant further investigation in the treatment of hypertension, are those that have manipulated dietary fat. It has been known for many years that pure vegetarians have a low incidence of hypertension (despite having high salt intakes), but the precise component that their diet contains to ameliorate any tendency for pressure to increase, or which pressor component of the omnivore intake is excluded from their diet, is uncertain. Studies increasing the ratio of dietary polyunsaturated to saturated fats have reported benefit in decreasing arterial pressure [7], but attempts to elucidate the mechanism by performing studies using supplements of linoleic acid have been negative for the most part. However the omega-3 fatty acids found in marine oils may hold more promise. Greenland Eskimos have a low arterial pressure and this has been ascribed in part to their consumption of raw fish. Three controlled studies suggest that fish or fish oils may be beneficial in hypertension [4], although the mechanism of action is not known at present.

In summary, it seems prudent to advise patients to control their body weight and restrict their sodium and alcohol intakes, and to encourage exercise. In the future, we may be able to recommend more explicit dietary supplements to reduce hypertension further without resort to pharmacological intervention.

Drug treatment of hypertension

In recent years the standard stepped-care drug regimen for hypertension has been reconsidered, with the introduction of newer agents into clinical practice. However, the publication of the results of trials of treatment for mild to moderate hypertension has led to renewed interest in medications which had fallen out of favour; this has been enhanced by the ever-increasing need to keep drug costs to a minimum. Therefore many practitioners have returned to beginning treatment with thiazide diuretics or β-blockers and combining the two agents, because the M.R.C. study suggests that they are safe, effective drugs, despite the tendency to metabolic changes in glucose tolerance and serum potassium and urate concentrations. Nevertheless, some patients find such drugs impossible to tolerate, or require increased medication to obtain control of arterial pressure.

The third line of treatment used to include hydrallazine or prazosin, but there is an increasing prescription of newer drugs. In this group two classes of agent have gained acceptance. The angiotensin-converting enzyme (ACE) inhibitors, captopril and enalapril, are used in combination with diuretics, β-blockers, or both. The early concern regarding the incidence of adverse effects has been reduced considerably with reductions in the maximum recommended dose [8]. In addition, despite claims that enalapril, without a sulphydryl group, would not have captopril-mediated side-effects, this has not proved to be true. Moreover, physicians are recognizing the problem of dry cough with captopril, which resolves promptly upon its withdrawal. Recently there have been reports of a small number of patients having developed angio-oedema with enalapril. Both drugs are useful also in the treatment of heart failure, and recent trials suggest that they may improve life expectancy in severe cases; enalapril is promoted as a once-daily preparation. Captopril was introduced originally for the treatment of severe hypertension refractory to other medications, although it is not totally successful in this type of patient [9]. Both captopril and enalapril seem better suited to mild or moderate hypertension.

The second group of drugs, the calcium channel antagonists are used also in mild cases of hypertension, although data suggest that these drugs are effective also in severe hypertension [10]. Three groups of calcium antagonist are available at present: phenylalkylamine group drugs such as verapamil, benzothiazepine derivatives such as diltiazem, and dihydropyridines such as nifedipine and related compounds such as nicardipine. Verapamil is a useful agent in the treatment of all forms of hypertension, although it is a negative inotrope and may precipitate heart failure and is best avoided in patients receiving β-blockers because of its effects upon the conducting system of the heart; in addition it induces intolerable constipation in a substantial proportion of patients. However, it appears to carry less risk of provoking the vasodilator side-effects of calcium antagonists such as headache, flushing, ankle swelling and burning sensation in the skin. Nicardipine and diltiazem have been introduced recently in the U.K., but the most frequently used drug is nifedipine. The combination of calcium antagonists and ACE inhibitors appears to be quite powerful and useful in moderate to severe hypertension [11]. More calcium antagonists are about to be introduced; whilst most will offer no benefits over the existing agents, manufacturers are aiming to produce once-daily preparations such as nitrendipine, and compounds without the side-effects which lead to 25% of patients being unable to tolerate these drugs at present.

Severe forms of hypertension refractory to conventional medication continue to be treated with minoxidil, although usually in combination with β-blockers and the large doses of loop diuretic needed to combat the fluid retention induced by the drug. However, such patients are in the minority, and the use of calcium antagonists has enabled many patients to avoid minoxidil which remains the most potent vasodilator in our armamentarium.

How far should arterial pressure be decreased?

Whilst recent studies have demonstrated unequivocally that satisfactory treatment of hypertension prevents stroke, the results in reducing deaths from myocardial infarction have been disappointing, and yet coronary events are the commonest complication of mild hypertension. This has posed many questions. Primarily, was the choice of treatment responsible for this failure? It has been suggested that β-blockers adversely affect the plasma lipid profiles, which would antagonize any benefit of decreasing arterial pressure. Similarly, diuretics increase blood sugar and decrease blood potassium. Recent studies have compared infarction rates between groups of patients receiving β-blockers and other treatments. In common with the M.R.C. study, the HAPPHY trial found no difference in infarction rate between those receiving thiazides or β-blockers [12]. Thus the putative "adverse" effects of β-blockers on serum lipids are unlikely to be important, or thiazide diuretics had equal effects, thereby failing to reduce coronary mortality via alternative mechanisms. Moreover, the publication of the HAPPHY trial seems to dim further hopes of a beneficial effect of decreasing arterial pressure upon the incidence of coronary events.

Two questions remain: first, is the incidence of coronary artery disease in hypertension irreversible? Second, is the decrease in arterial pressure attained by treatment too severe and perhaps detrimental to the heart in some patients? In response to the first question, there are data to suggest that patients with clinical evidence of ischaemic heart disease or cerebrovascular disease are more prone to further coronary events. Therefore, treatment of such patients' arterial pressure may be less beneficial than an assault upon an asymptomatic patient in whom there may be time and scope for reversing or retarding atherogenesis. In addition, hypertension is but one risk factor contributing to the increased incidence of vascular events. Smoking and serum cholesterol concentration are other factors which may dilute the benefit from antihypertensive measures if these are not independently attacked. However, it must be said that heart disease appears singularly resistant to antihypertensive regimens. The second question has become topical because of the recent trend to examine vascular complications at various strata of attained pressures after treatment. Some have argued that reducing diastolic arterial pressure to less than 85 mm Hg actually causes an increase in the incidence of coronary heart disease [13]. In line with this proposal, Strandgaard and Haunsø postulate that differences in autoregulatory reserve and blood oxygen extraction potential explain why antihypertensive treatment protects against stroke, but fails to reduce myocardial infarction [14]. In the brain, oxygen extraction from the blood can be increased if arterial pressure decreases below the lower limit of autoregulation. In the coronary circulation, oxygen extraction is nearly maximal at rest, so reduction of arterial pressure could lead to myocardial ischaemia [14]. The real benefit from treatment for stroke comes when the untreated diastolic arterial pressure is greater than 100 mm Hg. Therefore, mindful of the considerations above, it seems prudent to try and decrease sustained hypertension to between 90 and 100 mm Hg, and preferably to 90–95 mm Hg.

The future

Newer antihypertensive agents are being introduced into our clinical armamentarium: serotonin antagonists such as ketanserin appear to be effective in mild hypertension [15], although long-term studies are awaited concerning efficacy and tolerability, especially as headaches, dizziness and somnolence were problems until the recommended dose was reduced [15]. Currently, interest is being shown in agents which open membrane-located potassium channels. Pinacidil is available in Denmark and BRL34915 (Chromakalim) is undergoing trials in the United Kingdom [16]. Both may hold promise.

The cause of essential hypertension continues to frustrate those intent on searching for it. What has become clear recently is that medial thickening of the resistance arterioles is present, and in the established phase of the disease appears to be the only abnormality responsible [17]. Indeed, Folkow has demonstrated that such architectural changes could influence arteriolar haemodynamics so profoundly that almost no increase in vascular myocyte activity would be required to keep resistance to blood flow high in essential hypertension [18]. There are few data concerning direct measurements of resistance arteriolar morphology after a period of effective antihypertensive therapy. Indirect haemodynamic measurements would indicate that medication will regress the structural changes and data from genetically hypertension-prone mammals suggest that different drugs may have varying effects upon this medial thickening [19]. Recent data from direct measurements of morphology in human arterioles suggest that there is substantial reversal of these structural changes [19], and we eagerly await larger numbers to investigate whether one drug is superior to another.

Perhaps the future of pharmacological intervention in hypertension lies in anti-mitotic agents directed at the smooth muscle cell. Certainly there is still much to be accomplished in terms of therapy, both drug and non-drug related, with regard to trying to reduce the burden of coronary disease related to hypertension, and in terms of seeking the cause of this most common and potentially crippling disease.

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CORRESPONDENCE

UNILATERAL EXTRADURAL BLOCKADE IN OBSTETRICS

Sir,—The hypothesis advanced by Narang and Linter [1] concerning the cause of unilateral extradural blockade is intriguing. However, I must take exception to their mathematics. Using the data from their table I, I have calculated the percentage of unsatisfactory blocks at each S–EDS (skin–extradural space distance) (table I).

Spearman's rank correlation remains the same, but the authors' statement that there is a greater than 40% chance of producing an unsatisfactory block if the extradural space has not been identified before a depth of 6 cm, must be challenged. Calculations from their data (table I) put this figure at 33.7%.

S. Zbinden
Zurich

REFERENCE

1. Narang UPS, Linter SPK. Failure of extradural blockade in obstetrics. A new hypothesis. *British Journal of Anaesthesia* 1988; **60**: 402–404.

Sir,—Drs Narang and Linter [1] attempted to shed some light upon failed extradural blocks in obstetric practice and postulated that lateral placement of the catheter was responsible, resulting from deviation of the tip of the needle from the midline. Use of the paramedian approach may result in lateral placement of the catheter as or more frequently than the midline approach. However, in a prospective study of 165 patients, no difference was found in the incidence of failed blocks between the midline and paramedian approaches [2].

In obese patients, with a large skin to extradural space distance (and therefore greater likelihood of lateral placement of the catheter) there may be difficulty in location of the midline. The paramedian approach relies less upon identification of the midline [3] and, since the needle tip is angled medially after contact with the lamina propria, is unaffected by the skin to extradural space distance for placement of the catheter. Therefore, for patients in whom a large skin to extradural space distance is anticipated, the paramedian approach may be preferred.

TABLE I. *Numbers of unsatisfactory blocks*

	Unsatisfactory blocks (% of total number at each distance)	
S–EDS (cm)	My calculations	Narang and Linter table I [1]
2– < 3	0	0
3– < 4	12.5	14.4
4– < 5	14.1	16.4
5– < 6	18.3	22.4
6– < 7	31.1	45.2
7– < 8	38.3	62.2
8– < 9	41.7	71.4
9– < 10	0	0

R. M. Griffin
London

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Sir,—Dr Zbinden is correct. Unfortunately we made a transcription error and substituted failure/success % instead of failure/total % in column four of table I.

Our own preference for difficult obstetric extradurals is with the patient sitting. Scrupulous attention should be paid to monitoring a midline approach.

S. P. K. Linter
Southampton

PRICK TESTS TO DIAGNOSE ANAPHYLAXIS

Sir,—Following our study of prick tests in the diagnosis of anaphylaxis caused by general anaesthetics [1] we have simplified the method. In 34 patients (30 female, 4 male; ages 7–73 yr) who were referred to our department between April and June 1987 for skin tests to anaesthetics, we have compared prick tests with neuromuscular blockers (suxamethonium, gallamine, alcuronium, pancuronium and vecuronium) with prick tests that were made with a *mixture* of these same five drugs (final concentration = 1:5 of each).

Eleven patients who had an anaphylaxis (group 1) and 23 patients who had been previously anaesthetized without anaphylaxis (group 2), were considered by the anaesthetist to be "at risk".

In group 1, prick tests were positive (weal ⩾ 5 mm, flare ⩾ 10 mm) for at least one of the five neuromuscular blockers in all patients and positive with the mixture in 10. Prick tests were all negative in group 2 and so the results of the prick tests with the mixture were in agreement with those from the individual tests in 33/34 patients (Chi squared with Yates' correction = 24 8, $P < 0.001$).

This work shows that there was no haptenic inhibition with the mixture—that is, a neuromuscular blocker that did not give a positive result itself in a particular patient did not inhibit a positive reaction from another blocker in the same patient—and that a single prick test with a mixture of the compounds may be used to detect allergic patients (1 in about 3000) more easily and cheaply than with individual tests with each drug.

F. Leynadier
Paris

REFERENCE

1. Leynadier F, Sansarrico M, Didier JM, Dry J. Prick tests in the diagnosis of anaphylaxis to general anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 683–689.

CARDIAC ARREST FOLLOWING I.V. VERAPAMIL MAY BE RELATED TO CONCOMITANT DIGOXIN THERAPY AS WELL AS HALOTHANE

Sir,—The recent case report published in the Journal [1] attributed cardiac arrest during halothane anaesthesia to the drug interaction between halothane and verapamil. I would like to suggest that another drug which the patient was reported to be receiving might also be responsible for this unfortunate occurrence.

Exactly the same course of events has been reported in a patient who was being chronically treated with digoxin and received the same dose, 5 mg, of verapamil i.v., but who was not anaesthetized with halothane [2]. Although halothane can interfere in A–V conduction, interaction with verapamil is not as prominent as that seen with enflurane. Both our laboratory [3,4] and Kapur and colleagues [5] have reported this. However, in both instances very high plasma concentrations of verapamil were necessary for the interaction (greater than 200 ng ml^{-1}). In addition, the interaction of verapamil given i.v. in more than twice the dose reported in the letter [1] has been associated with minimal haemodynamic effects with MAC concentrations of all three inhalation anaesthetics [4,5]. Only the markedly invasive, highly instrumented preparation of Ramsay and colleagues [6] and the anecdotal observations of Prys-Roberts [7] have suggested a deleterious interaction between clinical concentrations of halothane and i.v. verapamil.

Obviously, a potent drug such as verapamil must be used with some caution at all times, and particularly during anaesthesia with the cardiac depressant inhalation anaesthetics. However, in my opinion, the conclusions of Møller are not justified by either his case report or a careful review of the literature [8].

R. G. Merin
Houston

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Sir,—Thank you for the opportunity to reply to the letter by Dr Merin.

I agree that the concomitant treatment with digoxin might have influenced the occurrence in the patient receiving i.v. verapamil followed by halothane anaesthesia, all three interfering with the A–V conduction.

However, also based upon the results of Chelly and colleagues [1] obtained in dogs, which was published after I submitted my letter, I still feel that my conclusion is valid: caution should be exercised in the simultaneous use of the two drugs—and especially so, if given in high doses.

I. W. Møller
Copenhagen

REFERENCE

1. Chelly, JE, Rogers K, Hysing ES, Taylor AS, Hartley C, Merin RG. Cardiovascular effects of interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. I. Verapamil and halothane. *Anesthesiology* 1986; **64**: 560–567.

DEADSPACE AFTER CORRECTIVE CARDIAC SURGERY

Sir,—Yates, Lindahl and Hatch [1] found a large increase in physiological deadspace after corrective cardiac surgery in children with left to right (LR) shunting. They suggested altered pulmonary wall tension and "different working conditions for the hypertrophic arteries" after correction as an explanation.

Fletcher and Jogi [2] reported similar findings in 13 children and adults, 10 of whom had atrial or ventricular septal defects (ASD). The changes were caused by variation in the alveolar deadspace fraction. Its mean value increased from 0.14 to 0.25 after cardiac bypass, and then decreased to 0.21 ($P < 0.01$).

The increase in alveolar deadspace was associated with a flat phase III of the single breath test for carbon dioxide. This relatively unusual combination of findings (increased deadspace is usually associated with an increased slope) is also seen in pulmonary embolism [3]. Therefore, we wondered if pulmonary air embolism was occurring during surgery. In two patients, Jogi was careful to vent the pulmonary artery and keep the tricuspid valve incompetent until the right atrium could be closed without admitting air; however, the increase in $V\mathrm{D}^{\mathrm{alv}}$ still occurred.

The suggestion that the changes might have been caused by a reduction in pulmonary artery wall tension was presumably made because most of Yates' patients had pulmonary hypertension. However, we saw the increase even in our youngest patients with ASD, and these probably had normal pulmonary artery pressures. The magnitude of the increase was not age-related and, therefore, probably not pressure-related. Quite possibly, the reduction in pulmonary *flow* (by a factor of 2–3 in most patients) was important for the observed transient failure of pulmonary capillary homeostasis. The flat single breath test phase III, typical also of hypoperfusion, supports this [4]. The improvement in gas exchange after sternal suture suggests that the lung quickly adapts to the reduced flow; ventilation is not a problem after operation.

Yates and colleagues [1] also found that carbon dioxide elimination during undisturbed anaesthesia was (insignificantly) lower in the cyanotic children than in those with LR shunting. Notwithstanding the lack of significance, the authors suggest that the difference was the result of less efficient ventilation in cyanotic children. This explanation implies that steady state had not been achieved at the time of measurement, and that carbon dioxide was being retained in these children, but not in the others. However, at the second measurement, Pa_{CO_2} was further reduced in the cyanotic children, and had increased in the others. The non-steady state explanation is therefore wrong. If there is a true biological difference, it may result from lower tissue carbon dioxide production. Is it not possible that cyanotic children consume less oxygen and, therefore, produce less carbon dioxide? My own preliminary results suggest that this may indeed be the case.

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HEAT AND MOISTURE EXCHANGERS

Sir,—We had been waiting with some interest for the publication of "Heat and moisture exchangers in artificial ventilation" by Tilling and Hayes [1] as this is the key reference to the test method used in *Health Equipment Information 166* [2].

The authors have designed a unique test apparatus in the belief that it is possible for patients to exhale air which is not fully saturated with water vapour. On basic physical principles this seems most unlikely: gas from a ventilated perfused alveolus must be fully saturated with water vapour; as this gas is exhaled it will cool by a few degrees, but will remain fully saturated.

In their discussion the authors admit that their unconventional hypothesis, that the exhaled air from patients can be significantly and variably desaturated, will be contested, but they say that only measurements on patients will settle the question. It is unfortunate that they did not consult the published literature before arriving at their hypothesis. Koch and colleagues [3] measured the temperature and humidity in a patient with a tracheostomy and with a heat and moisture exchanger (HME) fitted, and demonstrated that the expired air was fully saturated. Further confirmation is found in studies on patients in whom the trachea was intubated [4], who did not have the benefit of an HME: again, 100% saturation was found during expiration. Our initial studies with a modified commercial dewpoint hygrometer (Series 3000 Dew Point Meter, Mitchell Instruments Ltd, Unit 9, Nuffield Close, Nuffield Road, Cambridge CB4 1SS), not surprisingly, confirm that the expired air is effectively fully saturated when it leaves the tracheal tube in patients connected to an HME.

In the introduction the authors refer to two publications [5, 6] relating to "possible and actual drawbacks" of HMEs. Neither of these papers mentions such devices, let alone comments on their use. The first deals with the evaluation of heated humidifiers and the second is an investigation of the use of in-line breathing filters when using a hot water humidifier.

It is difficult to see the logic or practical value in that part of the investigation where the authors used a tidal volume of 54 ml when testing an HME with a deadspace of 97 ml [2]. It is not surprising that they describe the results of this part of the test as "interesting" and invoke either uptake of energy from the surroundings or an exothermic reaction to try to explain an apparent production of energy by the HME.

If there is interest in the function of a paediatric HME and the effect of leaks on its performance, the study by Gedeon and co-workers [7] used a model which gives a more accurate analogue to the clinical situation.

D. W. BETHUNE
R. D. LATIMER
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ACKNOWLEDGEMENT

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Sir,—Thank you for the opportunity of replying to Drs Bethune and Latimer. First, we must take issue with their statement that our paper is the "key reference to the test method used in *HEI 166*". This is not the case. As we pointed out in HEI, the method used to produce the results in that publication was closely modelled on that of Weeks and Ramsey [1], although we chose to use a humidity sensor which we had described elsewhere [2]. We constructed a new, somewhat simpler test rig to confirm a suspicion we had formed during our DHSS work that leaks between heat and moisture exchangers (HME) and our ISO test lung might be influencing the humidity delivered at the patient connection port of the system.

In our account of the method, we have stated clearly that water was introduced into our relatively crude lung simulator, the Lung Ventilator Function Analyser, to produce saturation of its contained gas by water vapour and that saturation was confirmed before and after each test. We think the sentence at the opening of our discussion may have been misinterpreted as a description of our method. What we wished to imply was that the generation of saturation at the point of production of humidified gas in such test rigs does not guarantee saturation under all conditions in adjacent parts of a dynamic system.

We did consult the literature, including the classic work of Déry and co-workers [3], as this has long been a natural starting point for any serious study of respiratory humidity, together with other sources confirming Déry's original observations. We agree that alveolar gas is almost certainly saturated with water vapour at the prevailing temperature, but that is not to say that, when gas is introduced into the large airways from the exterior and mixes with gas leaving the alveoli, this condition still obtains. The graph included in a communication from Drs Bethune and Shelly [4] confirms this, in that they showed the "humidity range in the upper trachea during inspiration with nasal breathing" to be in the range 56–78% R.H. at 37 °C, attributing this to Déry. We suspect that the hygrometer to which Drs Bethune and Latimer refer is insufficiently rapid in response to reflect the changing conditions and must be used outside the respiratory tract, albeit at a site in communication with it. Of course, any significant decrease in temperature will ensure saturation down-stream and we do not dispute that the gases reaching an HME are likely to be saturated, as we believe would have been the case in our study. Nevertheless, the water content at the lower temperature would be lower than that of gas saturated with water vapour at body temperature.

The reference [6] (DHSS, 1986) in connection with the "possible and actual drawbacks" of HME is correct. These appear on page 36 of HEI No. 166. We could also have added the DHSS's "Hazard" Health Notice HN(HAZARD) (85)7, referring to a problem with the proprietary device which Dr Bethune favours, but, instead, mentioned this also on page 36 of HEI No. 166. We think the title of Buckley's paper indicates its content and the reason for it having been cited. Moreover, he refers to the dangers of linking HMEs with heated humidifiers, a practice which has been indulged in by those believing that the output of HME might need to be supplemented.

The tidal volumes were representative values in the clinical range produced by the ventilator settings and have no individual significance. Although we knew that the ICOR HME for neonates was to be released, it was not on sale at the time of the study. Therefore, we used an adult HME which we knew to be one of the more efficient. It may be that the compressible volume which Drs Bethune and Latimer describe as "deadspace" could have had a detrimental effect on the results, especially in the case of the smallest delivered volume. Conversely, it might be argued that failure of some gas to pass out of the HME and re-enter it might have had the opposite effect. All we set out to show was that the presence of a leak detracted from the efficiency of an HME and that this might be in some way related to the magnitude of that leak. We have not purported to have discovered the reasons for the deterioration, other than the obvious one of gas lost from the system, but we tried to stimulate further interest by outlining the possibilities from a thermodynamic viewpoint. Further, all models thus far, including our own, are the crudest imitations of the lung itself and we believe we are right to say that work in human subjects is the only way to confirm the relevance of the findings for patients. In the meantime, we hoped that our work might alert practitioners humidifying patients with leaks around tracheal tubes to the possibility that values of humidity lower than those normally returned by their HME might apply. These circumstances are common in neonatal and small paediatric practice and the leak becomes more severe when compliance decreases or airways resistance increases.

The study by Gedeon, Mebius and Palmer [5] was not available to us when we submitted our paper for consideration, but we did refer to the new HME from ICOR, the subject of Gedeon's study, believing that it might show an improvement on its adult counterparts when specially designed for the application. We were, of course, delighted to learn that these workers had noted the same deterioration in performance when leaks were present and had investigated it independently, with conclusions similar to our own, but that the device had performed well under stringent test conditions.

We noted that HME are being used extensively and increasingly and that clinical experience in neonates in a centre of known excellence had been satisfactory [6].

We acknowledge the value of HME in many circumstances, but we do not accept that they are the only or necessarily the best answer to all humidification problems.

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POSTOPERATIVE PARAVERTEBRAL BLOCKS FOR THORACIC SURGERY

Sir,—We were particularly interested in the findings of Drs Conacher and Kokin's radiological study of paravertebral block [1], but feel that this is potentially misleading. Our observations from a continuing series of 45 cases of paravertebral block contrast significantly with the findings in their small study. Using a modification of Moore's technique we have injected 0.75% bupivacaine 5 ml, diluted with Conray 420, into the paravertebral space under x-ray control and observed the spread. We demonstrated a widespread distribution of contrast on A–P and lateral x-ray, as well as on CT scan, and this was confined to the paravertebral space in only 20% of cases. We have concluded that extradural spread is of more than "the occasional relevance" implied by the authors since this occurred in 70% of the patients in our series. Furthermore, it contributed significantly to the sensory blockade, which was more widespread in those with extradural spread than in those in whom paravertebral distribution occurred alone. Bilateral radiological spread of contrast was usually associated with ipsilateral analgesia.

We cannot agree with the authors' implication that disabling hypotension does not occur with paravertebral block. Profound hypotension, secondary to sympathetic blockade, occurred in 9% of our patients and was not always associated with demonstrable extradural spread.

We agree that the risk of intrapleural injection is substantial. However, none of the 7% with intrapleural spread in our series developed a pneumothorax. Pain relief in this latter group was very poor.

It may be that the different spread of contrast that we have noted is related to the different patient population rather than minor variations in technique. Our patients were not postoperative thoracotomy cases with potentially distorted tissue planes, but Pain Relief Clinic patients with undisturbed paravertebral anatomy. This would not support the authors' contention that extradural spread occurs only in the presence of pathology (e.g. fractured ribs).

We confirm the authors' finding that a single paravertebral injection provides excellent analgesia over several dermatomes, but the extent of the block is unpredictable and the risk of significant complications exists. We would also question the wisdom of paravertebral injection of neurolytic solutions—a technique sometimes advocated for terminal pain relief.

G. Purcell-Jones
D. M. Justins
London

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Sir,—Thank you for showing me the informative and informed comments of Drs Purcell-Jones and Justins. The correspondents have perhaps been a bit journalistically destructive by not quoting the sentence about relevance in full. It was not our intention to deny the possibility that extradural spread may occur in the absence of identifiable factors such as local trauma, but merely to point out that the presence of anatomical dislocation may make the extradural spread a preferential route on occasion. My impression from various studies and, in particular, from my own observations of resin injection in cadavers would confirm their view that extradural spread from paravertebral injection is more common than has been demonstrated radiologically heretofore.

Radiological contrast studies are often limited because spread of marker is only demonstrated in two dimensions and its actual site can only be presumed. My own resin studies confirm the cadaver ones of Moore [1] that significant spread occurs alongside and across the vertebral bodies where it may, as demonstrated *in vivo* [2], cross the midline. In this context, and I am hazarding guesses, it may be difficult to distinguish, from x-ray plates, whether spread is actually extradural or just confined to the sides or the fronts of vertebral bodies. The CT scans mentioned by the correspondents would therefore be very informative in defining whether extradural spread in some cases is actual or just apparent. I wonder if this may be one explanation for the clinical disparity between extradural spread of local anaesthetic being demonstrated radiologically and the finding that analgesia and sensory deficit are ipsilateral.

Turning to the issue of hypotension as a result of local anaesthetic paravertebral blockade that the correspondents have raised: we did not dispute that it occurs and that it may require treatment. The sentence in our study in which this facet is discussed does not contain a denial that significant hypotension occurs: it contains a comparison as rider, that the degree of hypotension is not as severe as that which was seen in a study made in thoracotomy patients who had extradural blocks. An emphasis on the potential for the development of hypotension is contained in the penultimate sentence of our study. Without discoursing on the mechanisms of this hypotension, it is my experience when performing paravertebral blocks in awake patients, that some develop hypotension as part of a vaso–vagal episode.

Of course, there is nothing new under the sun and we are all highlighting problems with paravertebral techniques that were apparent 40 and more years ago [3]. Clearly, the correspondents' experience, like our own, is that the thoracic paravertebral space, despite the idiosyncrasies of spread, is useful, if not the best, repository for drugs in some cases that come within the ambit of anaesthetists. It would seem that it is the common experience that injected substances frequently go beyond the bounds of the neat, definitive (and, for that matter, desired) anatomical locations adjacent to the thoracic spine, so that here at least Drs Purcell-Jones and Justins and I can concur, and question the wisdom of injecting drugs with irreversible, tissue destructive properties into thoracic paravertebral spaces.

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POSTOPERATIVE INTERCOSTAL BLOCK

Sir,—I read with interest the account by Baxter and colleagues [1] of their use of continuous intercostal nerve blockade after cardiac surgery. Their expressed intention was to study the effect of intercostal nerve blockade on pain relief and pulmonary function after cardiac surgery and to document the occurrence of any adverse effects they encountered. Whereas the excellent conduct of their trial allowed them to document their information accurately, I feel they have fallen prey to a very common fault of deriving incorrect conclusions based on the data they have collected.

It is well documented that patients undergoing major surgery suffer a reduction in respiratory capacity and that this may persist for quite some time after surgery [2–6]. To infer, as Baxter and colleagues did [1], that there is little to recommend intercostal analgesia over opioid analgesia merely because pulmonary function is not improved is quite erroneous. Based on their data, they may claim that intercostal nerve blockade provided significantly better pain relief than opioid analgesia and that, by their criteria, no improvement in pulmonary function was attended by this improved quality of analgesia. They may, therefore, conclude that there are factors other than improvement in pain relief which affect postoperative pulmonary function. This is already well documented. If they had looked at pulmonary function in the postoperative period before and after intercostal nerve block "top-ups" were required, these authors would have been able to document the precise effect of the nerve blockade on respiratory function, as this would have been the only variable. In my first paper on continuous intercostal nerve blockade [7], I measured respiratory peak flow in the postoperative period when further analgesia was requested and 30–40 min after the "top-up" was given. In these patients the peak flow improved by a mean of 37%. This is in direct conflict with the results of Baxter and colleagues but, unlike these authors, I can conclude that this effect must be a direct result of intercostal nerve blockade.

With regard to complications of intercostal nerve blockade, I feel that it should be stressed again that, based on the studies of Nunn and Slavin [8], it is clear that intercostal nerve blockade should be performed posteriorly at the site where the potential for pneumothorax is least, that is, where the rib is at its thickest. One can not recommend the injection in the mid axillary line as used by Baxter and colleagues.

Finally, the acceptability of performing intercostal nerve blockade in a patient in whom extradural analgesia is considered unsuitable because of prior administration of heparin must seriously be questioned, particularly in the light of the complication described by Baxter himself [9].

D. F. Murphy
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Sir—Thank you for the opportunity to reply to Dr Murphy's comments regarding our study on Continuous Intercostal Blockade after Cardiac Surgery [1]. Our intention was to assess this new technique objectively, as previous reports, including Murphy's own [2], have not been controlled or double-blind and are therefore subject to problems of bias, etc.

Pulmonary dysfunction after major surgery is already well documented, and we studied the effects of 36 h of continuous intercostal analgesia on the recovery of postoperative pulmonary function after cardiac surgery. From this point of view, it is irrelevant if there is a 37% improvement in peak flow after each "top-up" as Murphy found in his unblinded study (in a different patient population) which he quotes if, overall, this confers no significant improvement in the pattern of recovery, incidence of complications, and so on. Indeed, Murphy suggested in his paper that more studies are required to assess whether the technique actually reduces pulmonary complications; in this patient population it would appear that it does not.

We agree with Murphy that individual intercostal blocks are usually performed at the angle of the rib, and we changed our technique only for the purpose of convenience for this study. This did not appear to affect the efficacy of the blocks and, indeed, satisfactory analgesia was obtained. However, several reports have shown that good analgesia is produced with an intrapleural catheter [3–5]. Indeed, we have seen a few of our catheters within the pleural cavity and good analgesia was obtained after operation. In view of the controversy regarding the spread of local anaesthetic within the chest wall [6,7], could intrapleural spread of local anaesthetic be the mechanism of action of this technique? In any case, it does not appear to matter whether the catheter is in the "extrapleural space" or intrapleural to produce analgesia, but pneumothorax has been documented with a catheter in both sites.

Similarly, we do not advocate performance of these blocks in patients with a coagulopathy from any cause. All blocks in our study were performed after the coagulation profile had returned to normal, and in the patient with the complication to which Murphy refers, coagulation studies were normal before institution of the intercostal block. We know of no studies documenting the safety or otherwise of intercostal blocks with or without catheters after prior administration of, for example, low-dose heparin for DVT prophylaxis, although a conservative approach to this has been advocated by Bromage for extradural blocks.

The conclusion of our study was that, with intercostal catheters the patients may be more comfortable, but the recovery of pulmonary function in this patient population was no better than with i.v. narcotics, and we consider that, if the latter regimen had been optimized, it may have been as effective and a less invasive way of achieving the same degree of comfort.

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USE OF NALOXONE IN OPIOID-INDUCED ANAPHYLACTOID REACTION

Sir,—Mast cells have been shown to possess opioid receptors, and subcutaneous injection of endorphins, morphine, codeine and pethidine has been shown to cause weal reactions with mast cell degranulation [1]. We report a case of an anaphylactoid reaction to dihydrocodeine (DF 118) apparently responding to i.v. naloxone.

A 20-yr-old female with a family history of asthma was admitted 2 h after an overdose of an unspecified number of dihydrocodeine tablets. She was drowsy but co-operative. Pupil size was pinpoint, there was no sign of bronchospasm, and her heart rate was 90 beat min^{-1} with a systemic arterial pressure of 110/60 mm Hg. There was moderate facial oedema with a widespread urticarial rash, and a number of scratch marks were present. Naloxone 0.8 mg was given i.v. There was an immediate reversal of the drowsiness accompanied by pupillary dilatation. Within 15–20 min there was a reduction in vasomotor flushing and the patient reported a marked improvement in pruritus. Facial oedema improved over the next few hours. Peripheral blood eosinophil and C-1 esterase inhibitor concentrations were normal. Salicylate and paracetamol were not detected in blood.

Many clinical phenomena appear to involve mast cell degranulation without a clear relationship to allergy. These include cold, cholinergic and solar urticaria [2]. I.v. opioids induce increases in plasma histamine concentration in humans, confirming the capacity of these agents to cause mast cell degranulation [3, 4]. Naloxone by subcutaneous injection has been shown to inhibit morphine-induced weals, in a dose dependent manner [1]. The clinical response to i.v. naloxone seen in our patient is consistent with the above observations. We suggest that the use of i.v. naloxone in anaphylactoid type reactions produced by opioids may be beneficial, possibly by blocking further mast cell degranulation caused by circulating opioids.

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S. Burnett
B. G. Gazzard
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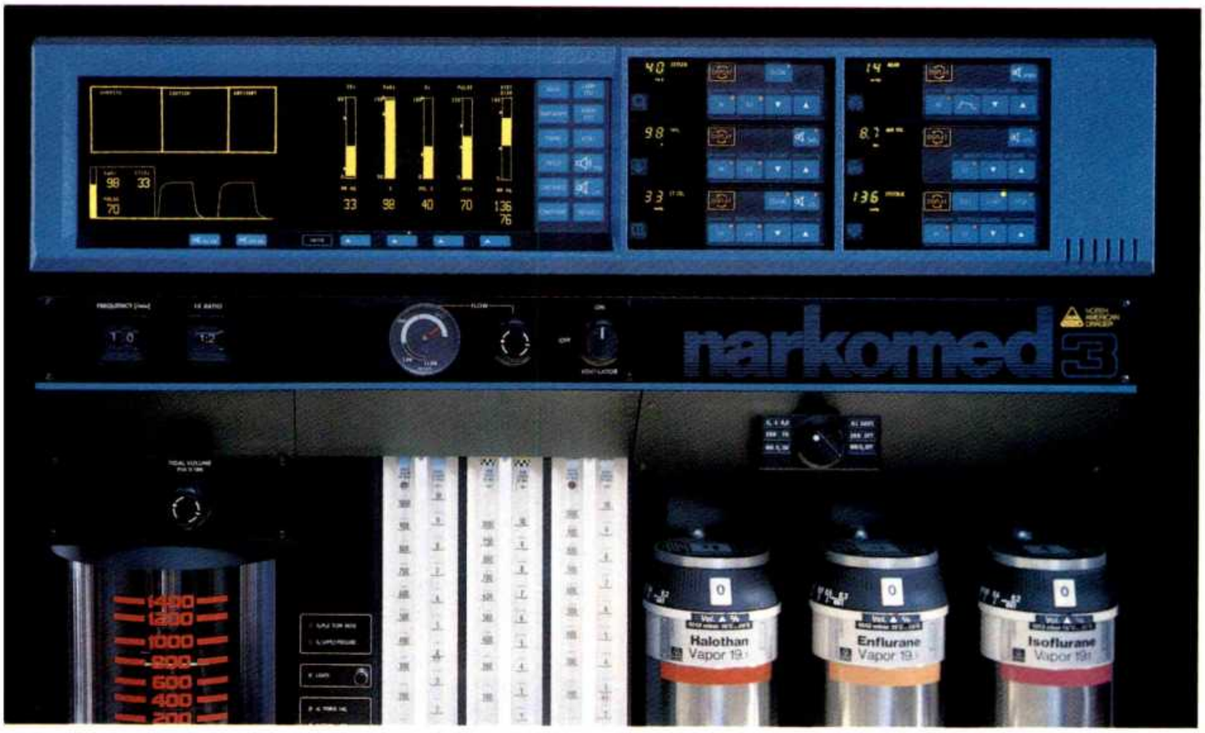

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British Journal of Anaesthesia

Editor: GRAHAM SMITH

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 61, No. 6 DECEMBER 1988

EDITORIAL

LOCAL ANALGESIC TECHNIQUES FOR UPPER ABDOMINAL SURGERY—ENDOCRINE AND METABOLIC EFFECTS

It is now more than 10 years since Engquist and colleagues observed that an extensive extradural blockade from T4 to S5 with 0.5% bupivacaine prevented the glucose and cortisol responses to hysterectomy [1]. They found that a less extensive blockade, for example from T8 to S5, abolished the increase in glucose but had little effect on the hypercortisolaemia in spite of providing excellent analgesia. The conclusion drawn from this study was that complete somatic and autonomic afferent blockade was necessary to prevent pituitary hormone secretion. On the other hand, the glycaemic response to surgery was mediated largely by stimulation of sympathetic efferent fibres to the adrenal medulla and liver. Since this seminal paper, Kehlet and colleagues have investigated exhaustively the effects of an extensive extradural block on the metabolic, hormonal, haematological and immunological responses to pelvic surgery [2–4]. This work has contributed greatly to our understanding of those aspects of the metabolic response to surgery which are mediated by afferent neuronal stimulation from the operative site and those which are mediated by cytokines such as interleukin-1. However, in upper abdominal surgery, extradural blockade is relatively ineffective.

In a classical paper in 1971 Bromage, Shibata and Willoughby [5] examined the effects of extradural blockade, up to the C6 dermatome, on the glucose and cortisol responses to upper abdominal and thoracic surgery. They found that the increase in blood glucose concentration was attenuated, but there was no effect on the increase in plasma cortisol concentration during and after operation. These findings have been confirmed in many subsequent studies and there is, at present, no local analgesic technique for preventing pituitary hormone secretion in response to upper abdominal surgery. What are the reasons for this difference between pelvic and upper abdominal surgery?

Bromage and colleagues suggested that the failure of extradural blockade to abolish cortisol secretion resulted from persistent vagal afferent activity from the upper abdomen or thorax [5]. However, attempts to establish vagal blockade together with thoracic extradural blockade before cholecystectomy failed to show any benefit over thoracic extradural analgesia alone [6]. Although parasympathetic afferent stimulation is an unlikely cause of pituitary secretion during upper abdominal surgery, it cannot be excluded. Inadequate sympathetic afferent blockade has been suggested as another possibility. It has been claimed that the addition of a splanchnic nerve block to a thoracic extradural block is more effective than extradural blockade alone in preventing the pituitary hormonal response to upper abdominal surgery, but the supporting evidence is inconsistent [7]. The current controversy over the level of sympathetic blockade compared with somatic blockade makes it difficult to infer adequate autonomic block from the dermatomal level [8].

The likelihood that somatic afferent blockade is incomplete in the presence of clinically effective extradural analgesia has been demonstrated recently using somatosensory evoked potentials [9]. In this study it was found that afferent neural stimuli passed through a supposed blocked area and that the use of pinprick to define somatic blockade was inadequate. Stimulation of the diaphragm and free nerve endings in the peritoneum have been invoked also as possible contributory causes to the endocrine response to upper abdominal surgery. Whilst the former is difficult to examine experimentally, Scott and colleagues in a recent issue of the Journal [10] showed that continuous i.p. bupivacaine had no effect on the cortisol response to cholecystectomy.

Thus the causes of the failure of thoracic extradural analgesia with local analgesics to prevent pituitary hormone secretion remain elusive, but the most likely factors are inadequate somatic and sympathetic afferent blockade. Improvements in analgesia by the addition of extradural opioids and systemic non-steroidal anti-inflammatory drugs do not ameliorate the endocrine response [11].

Several recent studies have examined other local analgesic techniques in upper abdominal surgery. Earlier this year in the Journal, Pither, Bridenbaugh and Reynolds [12] described the effects of an extensive bilateral intercostal block on the glucose and cortisol response to cholecystectomy. They observed a significant attenuation of the glycaemic response, and by inference provided sympathetic efferent blockade, but the increase in cortisol was not prevented. These results are strikingly similar to those obtained with thoracic extradural blockade and may be explained by spread of bupivacaine from the intercostal to paravertebral spaces [13, 14]. Therefore, endocrinologically and metabolically, a bilateral intercostal block will have effects similar to those of thoracic extradural blockade.

This issue of the Journal contains a description of another approach to the provision of analgesia for cholecystectomy, namely a right paravertebral block [15]. The results again show attenuation of the adrenaline and glucose responses with little effect on cortisol, although the number of intraoperative samples was small. The authors conclude that a paravertebral block acts as a "unilateral extradural", and anatomically this is entirely consistent with the known continuity between intercostal, paravertebral and extradural spaces.

Finally, intrapleural administration of bupivacaine has received enthusiastic support recently as a method of providing excellent analgesia after upper abdominal and thoracic surgery. Kehlet and colleagues have compared the effects of continuous extradural *v.* intrapleural bupivacaine on the hormonal and metabolic responses to cholecystectomy (personal communication). No differences between the two techniques were found and there was an increase in glucose and cortisol in both groups. It is assumed that, with the intrapleural technique, bupivacaine diffuses across the parietal pleura to act on the intercostal nerves. In the intercostal space the local analgesic is free to diffuse into the paravertebral and extradural spaces. This method of spread explains the bilateral segmental block of T4–T8 found with intrapleural bupivacaine in Kehlet's study, although this was much less extensive than the T4–T12 block observed in the thoracic extradural group.

In conclusion, bilateral intercostal blockade and unilateral paravertebral and intrapleural blocks have similar effects on the hormonal and metabolic responses to upper abdominal surgery and in this respect offer no advantages over thoracic extradural blockade. The results of these recent studies shed no light on the possible causes of the failure of local analgesic techniques to abolish the hormonal response to upper abdominal surgery. Their clinical usefulness will be determined mainly by the ease and safety with which they can be undertaken, but in most instances the dose of local analgesic is greater than that required for the equivalent extradural block. The questions posed by the study of Bromage and colleagues [5] still await an answer.

G. M. Hall and S. Lacoumenta

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PARAVERTEBRAL BLOCK DURING CHOLECYSTECTOMY: EFFECTS ON CIRCULATORY AND HORMONAL RESPONSES

K. GIESECKE, B. HAMBERGER, P.-O. JÄRNBERG
AND C. KLINGSTEDT

SUMMARY

Surgical trauma induces a hormonal metabolic response which is partly responsible for postoperative catabolism. In this study 12 patients underwent cholecystectomy during isoflurane anaesthesia, six with a paravertebral block (PVB) in addition. Plasma concentrations of glucose, cortisol and adrenaline, and heart rate and arterial pressure were compared between the two groups. The patients with PVB showed a significantly diminished response to noxious stimuli.

Paravertebral block (PVB) was described first in 1919 by Kappis [1]. It may be used for the same indications as intercostal extradural blocks, but has advantages such as a unilateral sympathetic blockade without the disabling hypotension found often when an extradural technique is used [2]. It is easy to perform and carries a small risk of complications [3, 4]. Several studies have demonstrated beneficial effects of extradural [5] and intercostal blocks [6–12] for postoperative pain relief and pulmonary complications. These advantages should hold for PVB in addition.

The complications reported for PVB include: total spinal block, headache, pneumothorax, and i.v. injection of local anaesthetic. The two former complications are probably more common when the medial technique [13] is used, while the risk of pneumothorax is greater with the lateral technique [14]. The overall frequency of complications accompanying PVB is not known. We have performed approximately 200 PVB, and have caused one small pneumothorax and a few instances of i.v. injection. None of these complications required treatment.

The present study was designed to examine the effect of PVB on the perioperative stress response to anaesthesia and surgery.

PATIENTS AND METHODS

Twelve healthy patients undergoing cholecystectomy through a subcostal incision were studied. All had given informed consent for the study, which was approved by the local Ethics Committee. Following i.m. premedication with morphine 0.15 mg kg^{-1} or ketobemidone 0.1 mg kg^{-1}, six of the patients received PVB with bupivacaine 20 ml. We used the lateral technique for performing PVB, as described by Eason and Wyatt [3].

All patients received general anaesthesia induced with thiopentone 3–5 mg kg^{-1} with atropine 0.5 mg and maintained with 1% isoflurane and 66% nitrous oxide in oxygen. Muscle paralysis was obtained with pancuronium 0.1 mg kg^{-1}. Residual neuromuscular blockade was antagonized at the end of operation with neostigmine 2.5 mg preceded by atropine 1 mg.

The left radial artery was cannulated with a 20-gauge Teflon catheter for continuous measurement of arterial pressure and sampling for blood-gas determinations. Intermittent blood samples were obtained for measurement of plasma catecholamine, cortisol and glucose concentrations at the following sampling times:

KAJSA GIESECKE, M.D., PER-OLOF JÄRNBERG, M.D. (Department of Anaesthesiology); BERTIL HAMBERGER, M.D. (Department of Surgery); Karolinska Institute, Karolinska Hospital, Box 60 500, S-104 01 Stockholm, Sweden. CHRISTER KLINGSTEDT, M.D., Department of Anaesthesiology, Karolinska Institute, Southern Hospital, Stockholm, Sweden. Accepted for Publication: January 8, 1988.

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TABLE I. *Patient characteristics (mean (SEM)). Anaesthetic time measured from start of anaesthesia to end of operation*

	n	Sex (M/F)	Age (yr)	Weight (kg)	Anaesthetic time (min)
Isoflurane	6	2/4	40 (6)	67 (7)	104 (19)
Isoflurane + PVB	6	2/4	45 (5)	71 (5)	87 (10)

(1) before induction of anaesthesia; (2) after induction of anaesthesia; (3) 1 min after tracheal intubation; (4) immediately before skin incision; (5) 1 min after skin incision; (6) during surgical exploration; (7) during surgical exploration.

Catecholamines were measured by high pressure liquid chromatography [15]. Cortisol was measured with radioimmunoassay [16] and blood glucose by a glucose oxidase method.

In the postoperative period, subjective experience of pain was measured by VAS (visual analogue scale), immediately after operation and then hourly until the patients felt pain and required analgesics.

Statistical analysis of data was performed using the Wilcoxon rank sum test and Mann–Whitney test as appropriate.

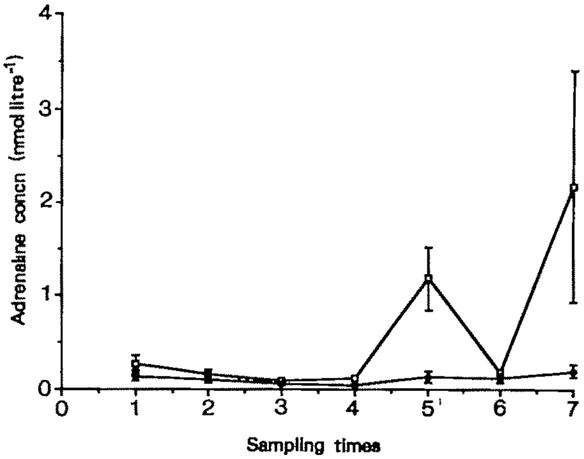

FIG. 1. Adrenaline concentrations for the isoflurane (□) and isoflurane + PVB (●) groups at the sampling times defined in the text. Bars represent SEM.

RESULTS

Details of the patients studied are shown in table I.

During the surgical procedure the plasma concentrations of adrenaline increased significantly from sampling times 1 to 7. In the

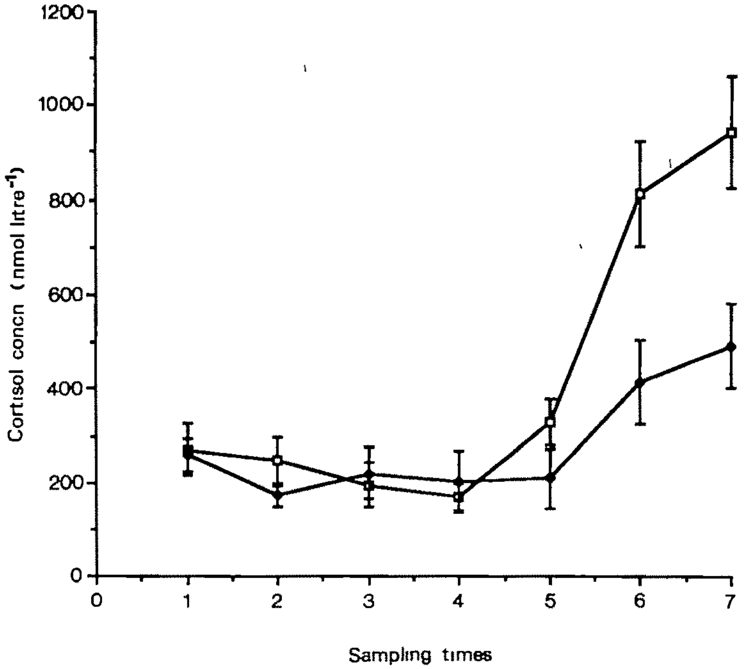

FIG. 2. Cortisol concentrations for the isoflurane (□) and isoflurane + PVB (●) groups at the sampling times defined in the text. Bars represent SEM.

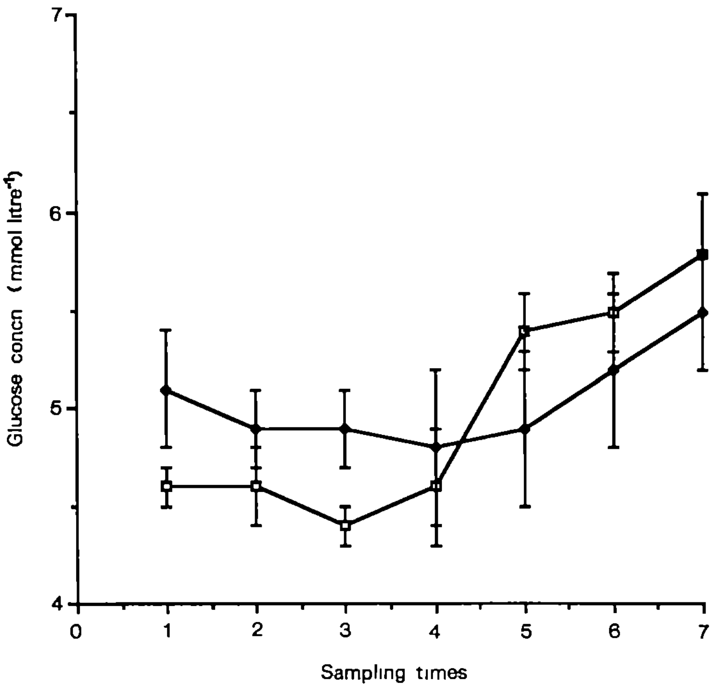

FIG. 3. Glucose concentrations for the isoflurane (□) and isoflurane+PVB (●) groups at the sampling times defined in the text. Bars represent SEM.

group given isoflurane only, there was a significant increase in plasma adrenaline concentration during surgical stimulation ($P < 0.05$) but this did not occur in the PVB group (fig. 1). There was a similar pattern for changes in plasma cortisol concentrations, with a significant increase only in the isoflurane group (fig. 2). For both groups, plasma glucose concentrations increased significantly ($P < 0.05$) during surgery. The increase in the isoflurane-only group was significantly higher than in the PVB group ($P < 0.025$) (fig. 3).

TABLE II. *Variations (mean (SEM)) in heart rate and arterial pressure (AP) in the two groups*

Sampling time	Isoflurane	Isoflurane+PVB
Heart rate (beat min^{-1})		
1	75 (6)	75 (6)
2	97 (4)	80 (6)
3	79 (4)	87 (8)
4	83 (4)	79 (7)
5	85 (5)	83 (10)
6	72 (6)	82 (8)
7	81 (10)	89 (8)
Systolic AP (mm Hg)		
1	126 (6)	139 (19)
2	143 (7)	150 (14)
3	90 (2)	143 (15)
4	99 (2)	92 (3)
5	122 (4)	111 (13)
6	100 (7)	121 (15)
7	123 (5)	118 (14)

There were no differences within or between the two groups in heart rate or systolic arterial pressure (table II).

The patients receiving PVB were completely free from pain for 1–6 h after operation.

DISCUSSION

The paravertebral space lacks well defined boundaries and it is therefore difficult to ascertain where injected local anaesthetic acts. The space communicates on the medial aspect with the extradural space and on the lateral side with the intercostal spaces [3, 17]. Recent studies have reported that radiopaque contrast medium from a PVB may enter the extradural space [18]. We believe that PVB acts as a "partial extradural". This assumption was confirmed by x-ray on two patients receiving PVB with contrast, which demonstrated a thin line of contrast medium laterally in the extradural space. This would explain its excellent analgesic effect across so many intercostal spaces without associated hypotension.

We have observed a significant increase in plasma concentrations of adrenaline, cortisol and glucose in patients given isoflurane only, but only for glucose in the patients who received an additional PVB. However, in the PVB group, concentrations of both cortisol and glucose increased slightly, suggesting only partial suppression of the stress response. A similarly differentiated stress response has been shown for other types of regional blocks [19,20].

It is surprising that the plasma adrenaline concentrations were low at point six. It is possible that the level of surgical manipulation was small at this point for most of the patients. The biological half-life of adrenaline (15 s) makes this hormone more susceptible than cortisol to variations in the degree of trauma.

We may conclude, therefore, that PVB attenuated the stress response occurring in cholecystectomy under isoflurane anaesthesia. This is in agreement with studies on extradural blocks extending to a high level (T5–S5) [21,22]. After operation, the PVB patients were entirely free from pain for 1–6 h, which is a shorter period than reported elsewhere [12,23].

Arterial pressure decreased in response to administration of isoflurane and remained at the same low value despite the higher concentrations of catecholamines in the isoflurane-only group. According to Stratton and colleagues [24] this lack of pressor effect from the higher catecholamine concentrations in the isoflurane-only group does not necessarily imply that there were no significant differences in other cardiovascular indices such as cardiac output, ejection fraction, stroke volume or systemic vascular resistance.

The patients who underwent surgery with the addition of PVB showed a significantly diminished response to noxious stimuli, both metabolically and clinically. We suggest, therefore, that PVB should be considered as an alternative to extradural and intercostal blocks for such operations. It is a good alternative to the use of opioids, since it is not associated with respiratory depression or postoperative drowsiness.

ACKNOWLEDGEMENT

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RESIN INJECTION OF THORACIC PARAVERTEBRAL SPACES

I. D. CONACHER

SUMMARY

Stained, quick setting resin was injected into the thoracic paravertebral spaces of six cadavers to assess the suitability of this material for delineating the spread of injected substances in an area of the human body which is being re-evaluated currently as a repository for analgesic drugs. The distribution and spread of the resin in relation to intercostal spaces, vertebral bodies and the spinal cord were noted, and compared with other studies.

Quick setting resins have been used extensively for making casts of anatomical structures and spaces [1]. In particular, they have been used to define aspects of the extradural space [2, 3]. These resins can be made suitable for injection through a needle, and stained to a colour that is visible when injected into areas covered by body tissues which are relatively transparent (e.g. the pleura).

Several cadaver studies have been conducted with dyes, stains and latex, injected extradurally and intercostally [4–7]. These have revealed the probable routes of spread of local anaesthetics when injected *in vivo*. The relationship between cadaver experiments and clinical practice has been confirmed in studies using radiopaque contrast media [6, 8], methylene blue [9] and radioactive markers [10]. In this last study, local anaesthetic reached the extradural space from intercostal space placement and a similar phenomenon was demonstrated when radiopaque contrast was injected in a thoracic paravertebral space [11].

Cross boundary spread to adjacent intercostal spaces, by local anaesthetic injected to an intercostal space, is a recognized phenomenon. Several routes have been delineated from cadaver and radiological studies. Spread may be across the internal surfaces of ribs [5], via a medial route from the point of injection along the intercostal space to the thoracic paravertebral space and from there caudad and cephalad to adjacent spaces [12], or through intervertebral foramina and up and down the extradural space [13]. Reports in the literature and experience from clinical practice suggest this last may be the least usual of the demonstrated routes.

MATERIALS AND METHODS

Permission to study cadavers about to undergo autopsy was sought from the local Department of Pathology. The project was approved by the Health Authority Ethics Advisory Committee. Before dissection, the cadavers were injected percutaneously with resin.

The reasons for using resin were (1) it was felt that resin, in common with latex but unlike the usual aqueous stains, would become fixed in position shortly after injection and set solid, so that further movement or artefactual spread would be less likely to occur when rough dissection, such as the removal of the vertebral bodies, took place; and (2) the potential for making casts of thoracic paravertebral spaces to demonstrate aspects of the relationships of their contents was considered worthy of assessment.

The landmarks used to approach the paravertebral space were those described by Eason and Wyatt [14]. Ten millilitre of resin mixture (Trylon Ltd, Wollaston, Northants, NN9 7QJ) was injected through a 14-gauge i.v. Teflon cannula and stilette placed through the

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skin at a point 2–3 cm lateral to the cephalad end of a palpable mid-thoracic spinous process. The needle was manipulated over the top surface of a rib and loss of resistance to the resin-mix injection sought as the needle point passed through the superior costo-transverse ligament and entered the paravertebral space. Injection was made at a rate of approximately 1 ml s^{-1}. In some cadavers the Teflon cannulae were left *in situ* to act as an internal marker for the sites of injection; as they are soft and flexible it was considered unlikely that they would injure the pathologist conducting the routine autopsy.

Approximately 2 h later, when the contents of the thoracic cavity had been removed, the anatomical distribution of the resin was noted. The vertebral bodies adjacent to the injection site were removed so that the spinal cord could be examined.

After some experimentation, the mixture that proved most effective, and most likely to set at the low temperatures encountered (approximately 4 °C) and within the time span available for investigation, was:

Crystic resin (Trylon CL201) 10 ml
Monomer C (Trylon Thinner) 5 ml
Accelerator E (Trylon Activator) 5 ml
Catalyst paste 2 g
Colour paste (mid-green) 0.5 ml

RESULTS

Six cadavers were studied (table I). In two, resin was found in the pleural cavity, and in two others it was found in the extradural space. There was no resin found across the midline. Spread in others was similar to that demonstrated radiographically *in vivo* [11]. Characteristically, injectate spread from the point of injection laterally along the adjacent intercostal space, in one case, as far as the level of the anterior axillary line. Anterior spread across the internal surfaces of the ribs close to injection point was demonstrated, as were cephalad and caudad spread from the paravertebral space to adjacent ones (fig. 1). In one case the range of spread was five spaces. In three of the five injections, correctly placed paravertebrally, injection dissected the pleural reflection from the vertebral bodies (fig. 2). Resin was seen extending across the lateral surfaces of as many as five vertebral bodies; in none of these did it cross the midline.

TABLE I. *Details of patients studied*

No.	Age (yr)	Sex	Site of spread	No. of locations
1	81	M	Paravertebral space	3
			Intercostal space	2
2	79	F	Paravertebral space	1
			Intercostal space	2
			Vertebral body	1
3	87	F	Pleural injection	
4	69	M	Paravertebral space	5
			Intercostal space	2
			Vertebral body	5
5 (fig. 1)	67	F	Paravertebral space	2
			Intercostal space	2
			Vertebral body	2
			Extradural spread	
6A	88	F	Paravertebral space	1
			Pleural injection	
6B (figs 2, 3)			Paravertebral space	2
			Intercostal space	2
			Vertebral body	2
			Extradural spread	

Dissection of the vertebral bodies adjacent to the small quantities of resin found in the extradural spaces of two of the cadavers demonstrated that entrance of resin was gained through the adjoining ipsilateral intervertebral foramen (figs 3, 4).

FIG. 1. Resin has spread from the paravertebral space (ps) into the one cephalad, and along the intercostal space (is) between the ribs (r) and on to the lateral surface of a vertebral body (vb).

FIG. 2. Extensive spread of resin along the intercostal space (is). The parietal pleura (pl) has been cut laterally at the point of injection. There is extrapleural spread across the inner surfaces of the ribs (r), and spread across the paravertebral space (ps) onto the vertebral body (vb), which has been dissected to expose the spinal cord (sc). Flecks of resin can be seen in the extradural space (es).

FIG. 3. A vertebral body (vb) has been cut, and a section displaced anteriorly and laterally (see figure 4) to demonstrate the intervertebral foramen (ivf) adjacent to the exposed spinal cord (sc). Flecks of resin, from the bolus injection into a paravertebral space medial to an intercostal space (is), are adherent to the intercostal nerve ganglion (ng), the anterior nerve root (ar), the posterior nerve root (pr), and the extradural space (es).

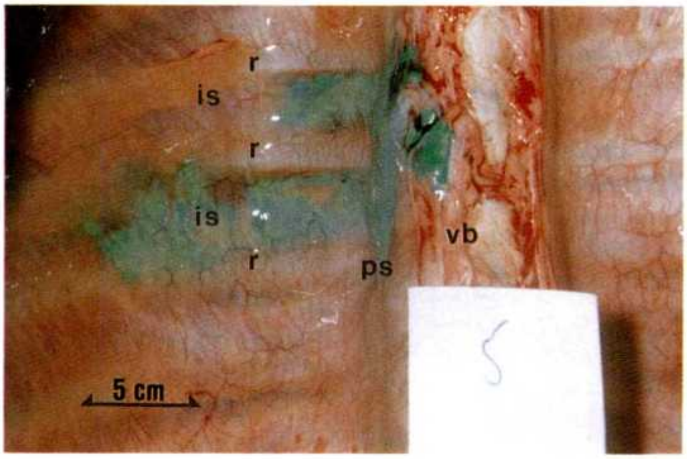

FIG. 1.

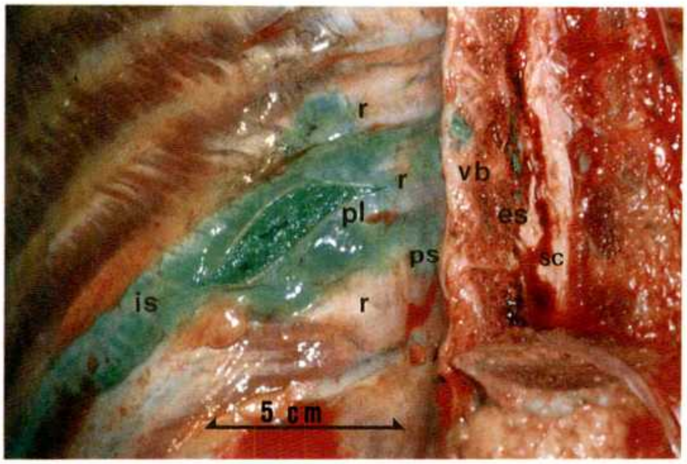

FIG. 2.

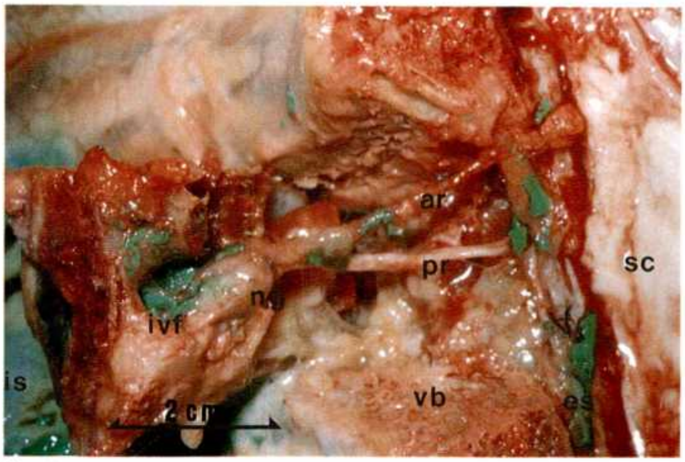

FIG. 3.

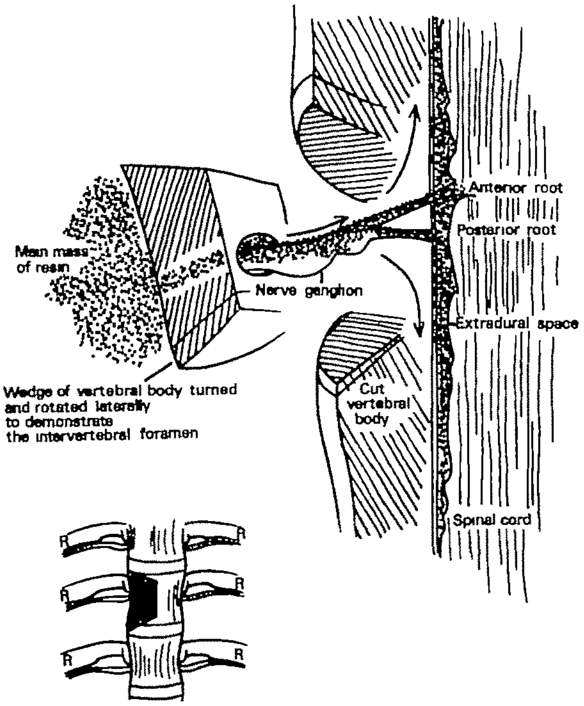

FIG. 4. Schematic representation of features demonstrated in figure 3. The route taken by resin spread from the paravertebral space is arrowed.

DISCUSSION

The injection of a resin rather than a dye or stain proved to have several advantages. Its tendency to gel rapidly limited excessive spread and staining of tissue zones under investigation, and its eventual solid consistency ensured that there was no further distortion or displacement during investigative dissection or examination manoeuvres. The nature of the material ensured that observations made were macroscopic and the relationship of injections to finer points of anatomical detail such as thin membranes, small nerves and fine muscle bundles, was impossible to elucidate. It is not clear if a flaw in the material, a property of the tissues of the paravertebral space, or a failure of the technique resulted in a spread of the resin too distantly, too diffusely and too widely to be useful for making casts.

There has been debate on the relevance of such studies to *in vivo* experience, where vital factors might influence the movement of injected substances [3]. Although the rate of injection of the resin and the pressure applied to the syringe were similar to those used by the author when injecting local anaesthetic into the thoracic paravertebral spaces of patients undergoing thoracic operations, extrapolation of the evidence obtained to situations *in vivo* must be made with caution. The resin mix is much more viscous than local anaesthetic solutions and, clearly, there is no mechanism for simulation of the mechanical and pressure effects exerted by functioning vascular and ventilatory systems, or the effects of cerebrospinal fluid dynamics; all may influence spread of injectate in the paravertebral spaces. However, there is much similarity between the findings in this study and an *in vivo* one using radiopaque contrast [11].

The main routes by which substances injected into the thoracic paravertebral space spread have been demonstrated again. These occur laterally along contiguous intercostal spaces, cephalad and caudad into adjacent paravertebral spaces, by sub-pleural dissection across the inferior surface of ribs, across the lateral surfaces of the posterior parts of the vertebral bodies, and into the extradural space.

A clinical study [9] using bupivacaine and methylene blue suggested that spread of injectate across vertebral bodies may account for the occurrence of the extradural block from intercostal injection as reported, for instance, by Middaugh and colleagues [10]. In the study of Moore, Bush and Scurlock [6], spread of marker across the midline over the anterior surfaces of the vertebral bodies did not occur from intercostal injection, but such spread was noticed by the authors of an *in vivo* study [9]. In this cadaver study, utilizing a 10-ml bolus injection, spread across the surfaces of vertebral bodies occurred in some cases more anteriorly than noted by Moore, Bush and Scurlock, but the resin did not cross the mid-line in any of the cases. The only demonstrable connection between the paravertebral space and the extradural space was that through the ipsilateral intervertebral foramen.

In current practice, intercostal and paravertebral blocks, with or without catheters, are used largely to provide postoperative or post-traumatic pain relief. Extradural blockade is one of the complications of which most operators are aware. Consideration of the number of complications of these blocks reported in the literature of the past decade suggests that extradural block may be a rare event. Entrance of resin into the extradural space occurred in a significant proportion of the cadavers studied here, but the amount of resin seen was only a small proportion of the original 10-ml bolus. The implication of this evidence is that extradural spread of injectate may be more common than has been assumed. This potential should be borne in mind when local anaesthetics or, as recently reported [15], opioids are deposited close to the thoracic paravertebral space.

ACKNOWLEDGEMENT

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SUFENTANIL AND NITROUS OXIDE ANAESTHESIA FOR CARDIAC SURGERY

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SUMMARY

We have investigated the use of sufentanil 3.75–15 μg kg^{-1} by supplementing anaesthesia with nitrous oxide and midazolam. Thirty patients with ejection fractions exceeding 30% were studied while undergoing scheduled coronary artery vein graft surgery. Even in the lowest dose group (3.75 μg kg^{-1}), haemodynamic responses to surgical and anaesthetic stimuli were sufficiently obtunded that no patient exhibited an increase in heart rate or systolic arterial pressure greater than 20% of the control value. Marked hypotension occurred in some patients during unstimulated periods. Such periods of hypotension were associated with equally marked decreases in systemic vascular resistance. The mean recovery times to spontaneous ventilation after the end of surgery ranged from 6 to 12 h. This is longer than would be expected from other studies using a similar dose of sufentanil. This may be related to the use of benzodiazepines during anaesthesia and to their use after surgery in those patients who became restless.

The ability to obtund cardiovascular responses to surgical stimuli may be an intrinsic property of very potent opioids [1]. Sufentanil is a potent opioid analgesic relatively recently introduced into anaesthetic practice [2]. Its higher potency and shorter elimination half-life [3] when compared with fentanyl [4] may make it a more suitable drug for cardiac anaesthesia. Indeed, it has been shown in a comparative trial, that sufentanil 12–30 μg kg^{-1} has a superior modifying effect on cardiovascular responses compared with fentanyl in doses up to 120 μg kg^{-1} [5]. However, neither Rosow and colleagues [6] nor Howie and co-workers [7] using similar dose ranges were able to show any significant differences between the two drugs.

One would expect the shorter half-life of sufentanil to confer an advantage in clinical practice, as there is a trend towards progressively earlier extubation of the trachea after cardiac surgery. However, there are conflicting reports about the clinical significance of the shorter half-life of sufentanil when compared with fentanyl. For example, Howie and co-workers [7] and de Lange and associates [5] found no difference in recovery times; Sanford and colleagues [8], using the same dose as Howie and co-workers [7], found that recovery from sufentanil was significantly quicker. However, there were some differences in premedication and method of sufentanil administration that could account for this discrepancy.

These previous studies have been conducted using opioid–oxygen anaesthesia. There have been few studies of the cardiovascular effects of the combination of sufentanil and nitrous oxide (in oxygen). When used in balanced anaesthesia with nitrous oxide, relatively low doses of sufentanil (2.5 μg kg^{-1}) have been associated with suppression of cardiovascular responses to surgical stress in patients undergoing non-cardiac surgery [9].

The present study was designed to investigate the effects of three different doses of sufentanil, during balanced anaesthesia with nitrous oxide, on the haemodynamic responses and the recovery times in patients undergoing cardiac surgery. The

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aim was to determine if balanced anaesthesia with an appropriate dose of sufentanil plus nitrous oxide produced a stable anaesthetic, compatible with early recovery.

PATIENTS AND METHODS

Following Ethics Committee approval, informed consent was obtained from 30 patients with left ventricular ejection fractions exceeding 30% and who were scheduled to undergo coronary artery vein graft surgery (CAVG). They were allocated randomly to three equal groups to receive sufentanil as follows: group 1, 3.75 µg kg^{-1}; group 2, 7.5 µg kg^{-1}; group 3, 15 µg kg^{-1}.

Patients were premedicated with diazepam 15–20 mg by mouth followed by papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. Half their normal daily dose of beta-adrenoceptor blocking agent was given with their normal morning dose of calcium channel blocker, when relevant.

Pulmonary artery and radial artery catheters were inserted under local anaesthesia before the induction of general anaesthesia. Five minutes later, standard haemodynamic variables were measured at the following times:

Event 1 = baseline
Event 2 = 2 min after induction of anaesthesia
Event 3 = 2 min after administration of sufentanil
Event 4 = 2 min after intubation
Event 5 = 2 min after skin incision
Event 6 = 2 min after sternotomy

The standard haemodynamic variables measured were heart rate, systemic and pulmonary artery pressures, right atrial pressure, pulmonary artery wedge pressure and cardiac output. Other data (stroke work indices, vascular resistances) were derived using standard equations.

Anaesthesia was induced with midazolam 1–4 mg. Pancuronium was administered in a dose of 0.1 mg kg^{-1}; two-thirds of the sufentanil dose was administered at 2.5 µg kg^{-1} min^{-1}. The lungs were

TABLE I. *Cardiovascular variables for group 1 sufentanil 3.75 µg kg^{-1}; group 2 sufentanil 7.5 µg kg^{-1}; group 3 sufentanil 15 µg kg^{-1}. SVR = Systemic vascular resistance; CVP = central venous pressure*

	Group	Baseline	After midazolam	After sufentanil	After intubation	After first skin incision	After sternotomy	95% Confidence values
Heart rate (beat min^{-1})	1	54.8	55.9	59.8	60.7	54.7	56.7	±4
	2	62.3	60.3	64.7	67.7	63.9	62.8	
	3	52	52.3	55.2	51.2	54.5	52.5	
Systolic arterial pressure (mm Hg)	1	116.6	113.8	87.4	98.4	96.6	110.7	±7.4
	2	134.7	124.0	94.5	98.6	100	116.5	
	3	123	119	101	106	97	103	
Mean arterial pressure (mm Hg)	1	80.4	80.5	61.7	70.8	72.4	83.4	±6.4
	2	84.2	85.6	68.5	71.9	74 2	84.8	
	3	83.8	79.3	68.6	76.2	71.7	76.3	
SVR (dyn s cm^{-5})	1	1258	1371	1206	1057	1347	1582	±160
	2	1369	1413	1026	1045	1326	1441	
	3	1242	1277	987	1008	1298	1398	
Systolic pulmonary artery pressure (mm Hg)	1	28.1	30.6	27.9	30.2	23.3	26.1	±2.5
	2	30.9	28.4	29.5	23.4	23.4	23.5	
	3	28.6	28.6	32	23.2	26.5	26.5	
Mean pulmonary artery pressure (mm Hg)	1	19.1	18.8	17.6	19.6	15	18.2	±2
	2	20.6	19.6	20	19.6	15.2	15.9	
	3	17.6	17.5	18.2	20.2	15.3	18.3	
Pulmonary capillary wedge pressure (mm Hg)	1	10.4	10.6	9.7	9.7	9.0	11.8	±1.6
	2	13	12.8	11.5	10.6	9.9	10.0	
	3	10.7	11.4	11.2	10.7	8.0	10.9	
CVP (mm Hg)	1	6.4	7.1	6.1	6.4	5.6	6.1	±1.6
	2	7.1	8.0	7.7	6.9	5.3	5.5	
	3	6.5	7.9	6.9	6.5	6.6	8.9	
Cardiac output (litre min^{-1})	1	4.9	4.4	4.1	5.0	4.1	4.0	±0.38
	2	4.9	4.5	4.8	5.1	4.4	4.5	
	3	5.1	4.6	5.1	5.6	4.2	4.0	

ventilated with 60% nitrous oxide in oxygen as soon as anaesthesia commenced. Before sternotomy, the remainder of the sufentanil was given. A further bolus of midazolam 5 mg was given on establishing cardiopulmonary bypass (CPB).

The times after the end of surgery were noted for the return of consciousness and of spontaneous ventilation, the latter defined by satisfactory blood-gas tensions (Pa_{CO_2} < 45 mm Hg and Pa_{O_2} > 85 mm Hg) without prompting.

Statistical analysis was by repeated measures analysis of variance. The data do not fulfil the requirement of conventional analysis of variance because the individual data points in our study are not independent. Significant differences were further investigated by multiple *t* testing and the *P* values corrected by Bonferroni's adjustment.

RESULTS

The three groups of patients were not statistically different with respect to age, weight and sex. Measured and derived cardiovascular indices are shown in table I. Statistical analysis of the cardiovascular variables showed significant changes within the three groups associated with anaesthesia and surgery, but only the left ventricular stroke work index (LVSWI) differed significantly between groups.

There was a statistically significant increase in heart rate after the administration of sufentanil and intubation, but this was small and of the order of 5–7 beat min^{-1} (fig. 1). Systolic arterial pressure and systemic vascular resistance (SVR) showed a uniform trend during the procedure, with no significant differences between any of the groups (figs 2, 3). There was a marked decrease in systolic arterial pressure after the administration of sufentanil, associated with a similar decrease in SVR. There was very little change in systolic arterial pressure after intubation and a small increase towards pre-induction values after sternotomy. Left ventricular stroke work index showed a modest decrease associated with anaesthesia (fig. 4). There was a significantly greater decrease in group 1 than in group 3 after sufentanil administration, and a significantly greater decrease in group 2 compared with group 3 after intubation.

Recovery times showed highly significant differences between the three groups: mean times for spontaneous ventilation to resume were 6.1 h for group 1, 9.1 h for group 2 and 12.0 h for group 3 (fig. 5).

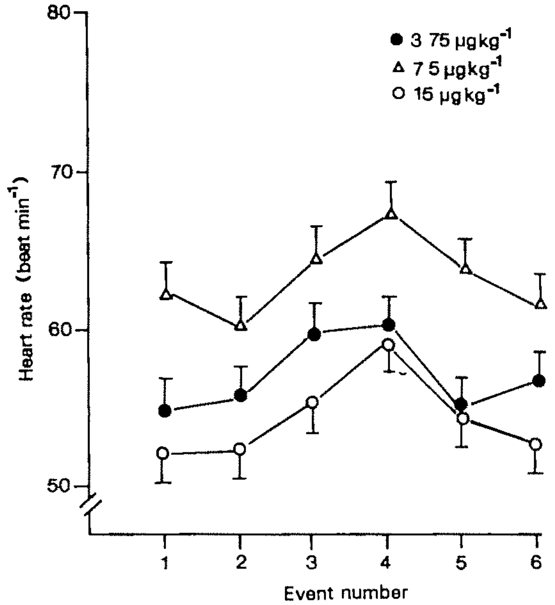

FIG. 1. Heart rate during anaesthesia with three different doses of sufentanil and surgery. Event 1 = baseline; event 2 = after midazolam; event 3 = after sufentanil; event 4 = after intubation; event 5 = after first skin incision; event 6 = after sternotomy. Values are means (with one SE shown). *F* value for difference between groups: 1.61 ($P = 0.21$). *F* value for differences within groups: 5.53 ($P = 0.0008$).

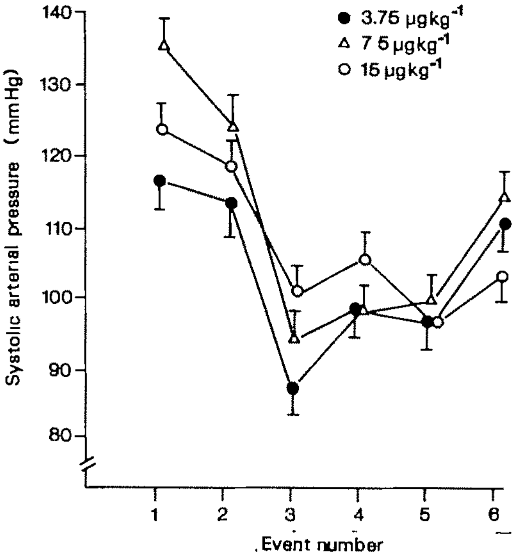

FIG. 2. Systolic arterial pressure during anaesthesia with three different doses of sufentanil and surgery. Event 1 = baseline; event 2 = after midazolam; event 3 = after sufentanil; event 4 = after intubation; event 5 = after first skin incision; event 6 = after sternotomy. Values are means (with one SE shown). *F* value for differences between groups is 0.69 ($P = 0.51$). *F* value for differences within groups is 31.8 ($P < 0.0001$).

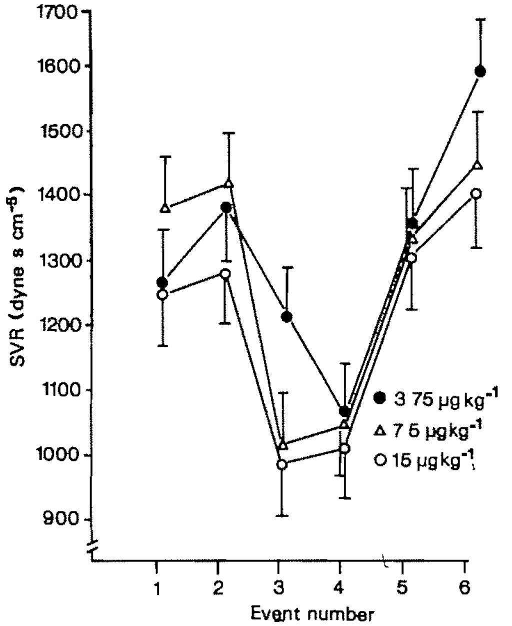

FIG. 3. Systemic vascular resistance during anaesthesia with three different doses of sufentanil and surgery. Event 1 = baseline; event 2 = after midazolam; event 3 = after sufentanil; event 4 = after intubation; event 5 = after first skin incision; event 6 = after sternotomy. Values are means (with one SE shown). F value for differences between groups is 0.76 ($P = 0.48$). F value for differences within groups is 12.6 ($P < 0.0001$).

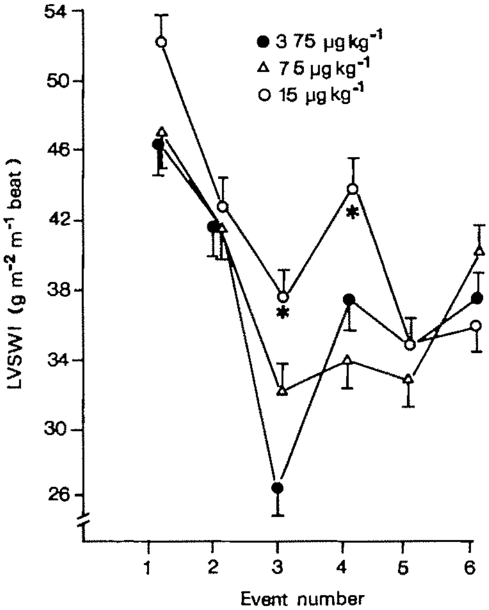

FIG. 4. Left ventricular stroke work index during anaesthesia with three different doses of sufentanil and surgery. Event 1 = baseline; event 2 = after midazolam; event 3 = after sufentanil; event 4 = intubation; event 5 = after first skin incisions; event 6 = after sternotomy. Values are means (with one SE shown). * Significant difference between group 1 and group 3 at event 3, and group 2 and group 3 at event 4 (adjusted P values < 0.0005).

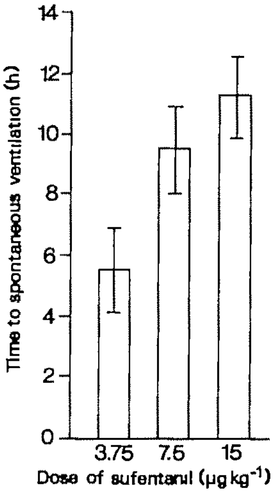

FIG. 5. Time to establish spontaneous ventilation after surgery. Times are hours after end of surgery (with one SE shown).

DISCUSSION

One problem of cardiac anaesthesia is how to suppress cardiovascular and hormonal responses to surgical stimuli and simultaneously provide a stable cardiovascular system during rapidly changing degrees of stimulation. Whilst inhalation agents can provide satisfactory conditions for cardiac surgery, their use requires considerable "fine tuning" [10]. In 1969, Lowenstein and colleagues [11] investigated the haemodynamic changes associated with large doses of morphine in cardiac patients. They demonstrated that morphine 0.5–3 mg kg^{-1} had no depressant effect on cardiac function and that, in patients with valve disease, the vasodilator properties of morphine actually promoted an increase in stroke volume. In addition, in most patients there was a high degree of cardiovascular stability. Since then, anaesthetists have shown increasing interest in high-dose opioids to provide stable cardiovascular conditions. High-dose morphine has been superseded by the newer opioids, mainly because of the extremely long period of emergence from morphine anaesthesia [8]. The use of fentanyl in cardiac surgery has been extensively researched both as a high-dose sole anaesthetic and as an analgesic supplemented with nitrous oxide, benzodiazepines or inhalation agents [12].

Some workers have found high-dose fentanyl–oxygen anaesthesia only partly successful in blocking the cardiovascular and hormonal responses to surgery [5, 13]. Others have found that fentanyl effectively obtunded these responses [14, 15]. However, the studies are not strictly comparable. Patients in the latter study [15] were undergoing mitral valve surgery and not CAVG surgery. There were also differences in the premedication regimens: patients in the former group [14] received nitrous oxide, while half of the patients in the second study [15] were given diazepam during the surgical procedure.

Sufentanil is a potent opioid (about seven times as potent as fentanyl) and has been studied in cardiac surgery as an alternative to fentanyl. The effects on the suppression of hormonal responses in the period before bypass have been encouraging [16], but may not be better than fentanyl [7]. However, the effects of sufentanil on cardiovascular dynamics are less certain. Some researchers using sufentanil at a dose between 11 and 30 μg kg^{-1} have found little difference between this drug and a comparable dose of fentanyl [6, 7]. However, de Lange and co-workers [5], using sufentanil 12 μg kg^{-1}, did find a significant advantage over fentanyl. They found that the sufentanil group required significantly less vasodilator therapy for hypertension compared with the fentanyl group. Furthermore, they noted that patients in the sufentanil group who were receiving preoperative beta-adrenergic blockers required no vasodilator intervention. Elsewhere, Stanley, de Lange and Boscoe [17] have commented on the reduction of opioid requirements in patients receiving beta-blockers before operation.

None of our patients exhibited any hypertensive responses at any time. On the contrary, there was a significant decrease in systolic arterial pressure after the induction of anaesthesia; this was marked in two patients who needed a vasopressor. Marked decreases in systolic arterial pressure associated with sufentanil have been described previously [18, 19] when i.v. benzodiazepines were used in the anaesthetic sequence. The decrease may be partly associated with experimental design creating unusually long periods without stimulation.

The changes in heart rate were also minimal and were probably associated with the vagotonic effects of sufentanil. In spite of the concomitant administration of pancuronium, three patients required vagolytic drugs. There was thus a small increase in mean values of heart rate after sufentanil administration (and after intubation). Previous research has shown that, where pancuronium is given before sufentanil, serious bradycardia does not occur, but a similar increase in heart rate still occurs [20]. They found that bradycardia requiring vagolytic drugs occurred with atracurium and vecuronium when anaesthesia was induced with sufentanil 15 μg kg^{-1}.

The LVSWI was the only haemodynamic index to show any significant differences between the groups. There was a 40% decrease in group 1 after induction and a significant difference at this point between groups 1 and 3. This may be partly explained by group 1 patients also exhibiting the greater decrease in systolic arterial pressure. Changes in LVSWI are difficult to interpret as the index fails to differentiate between (useful) flow work and (wasteful) pressure work.

The marked suppression of cardiovascular responses in our study is probably associated with the use of nitrous oxide and midazolam. Interactions between opioids, nitrous oxide and benzodiazepines have been well described. Tomichek and colleagues [21] described marked hypotension when diazepam was given before high-dose fentanyl. This was associated with equally marked decreases in systemic vascular resistance and, interestingly, marked decreases in plasma catecholamine concentrations. Stroke volume index was, however, unchanged. Other reports [22] suggest direct myocardial depression. The effects of nitrous oxide–opioids have also been well described. McDermott and Stanley [23] found a 36% decrease in stroke volume with 50% nitrous oxide and morphine. Lappas and co-workers [24] found a 21% decrease in stroke index using 50% nitrous oxide, but this was associated with a decrease in the rate–pressure product. This impairment may occur only in patients with coronary disease and high left ventricular end diastolic pressure [25, 26]. Of greater concern is the potential for nitrous oxide to create ischaemic conditions in cardiac patients anaesthetized with opioids [27, 28].

The interaction between nitrous oxide and midazolam should be considered. Samuelson and associates [10] found the effect of nitrous oxide on an induction dose of midazolam innocuous in cardiac patients. Falk and co-workers [29] reported a case of marked vasodilatation with diazepam and nitrous oxide during induction of anaesthesia.

The recovery times after high dose sufentanil–oxygen anaesthesia are sometimes still prolonged in spite of its slightly shorter half-life. Comparing sufentanil with fentanyl, Howie and colleagues [7] and de Lange and co-workers [5] found no significant difference in recovery times. Sanford and associates [8] found that patients given sufentanil breathed spontaneously and could have the tracheal tube removed significantly sooner than those given fentanyl.

Our times for the return of spontaneous ventilation were significantly different between groups and this is obviously a dose-related effect. Mean recovery time after sufentanil 15 μg kg^{-1} was 11.7 h. This is long compared with 5.6 h in Sanford's group (given 15 μg kg^{-1}) or de Lange's group (given 12 μg kg^{-1}). Howie and colleagues [7] using orientation as the endpoint, found mean recovery time was 7 h after 20 μg kg^{-1} and mean extubation time was 17 h. We decided to take spontaneous ventilation as our endpoint rather than extubation, as the latter depends on a variety of factors including patient build, preoperative respiratory status, and the absence of surgical bleeding. Even our low dose group (sufentanil 3.75 μg kg^{-1}) took 5.7 h (mean) to resume spontaneous ventilation. Our premedication probably produced greater sedation than that in the three other groups described earlier. Unlike them, we used a combination of an opioid and a benzodiazepine as premedicant. In addition, midazolam was given for the induction of anaesthesia and before the start of cardiopulmonary bypass. Some patients also received small boluses of midazolam in the early postoperative period. They were clearly free of pain, but awoke extremely restless and confused. Thus in our patients we did not find our technique compatible with a policy of early extubation.

Sufentanil, even in our lowest dose of 3.75 μg kg^{-1}, provided a satisfactory suppression of cardiovascular responses. It would be interesting to substitute a potent inhalation agent for both nitrous oxide and midazolam and to observe whether similar haemodynamic trends prevailed. If so, concerns about nitrous oxide and myocardial metabolism could be forgotten and a decrease in the dose of midazolam may allow earlier recovery.

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SEDATION FOLLOWING CARDIAC SURGERY: EVALUATION OF ALFENTANIL AND MORPHINE IN THE PRESENCE OF A COMPUTERIZED CLOSED LOOP ARTERIAL PRESSURE CONTROLLER

I. M. McMENEMIN, J. A. CHURCH AND G. N. C. KENNY

Following coronary artery surgery, most patients undergo intermittent positive pressure ventilation (IPPV) electively for a period. Correct assessment of pain and distress in such patients is based on appearance and cardiovascular changes such as hypertension and tachycardia. However, despite apparently adequate analgesia, after coronary artery surgery a large proportion of patients develop hypertension which requires vasodilator therapy such as an i.v. infusion of sodium nitroprusside (SNP) [1].

The ease of control of hypertension using vasodilators may be a useful method of assessing the adequacy of sedation and analgesia. Measurement of this is possible using a computer-controlled closed loop system such as that developed by Reid and Kenny [2], which controls arterial hypertension with an infusion of SNP.

An appropriate method of providing adequate analgesia and sedation to prevent inappropriate swings of arterial pressure following stimuli such as tracheal suction or changing position may be an infusion of alfentanil, an opioid with rapid onset and short duration of action. This would allow adequate analgesia when appropriate, and permit rapid recovery after the infusion was discontinued. Yate and colleagues [3–5] have described such infusions for sedation and analgesia in intensive care units (ICU).

SUMMARY

Forty patients who had undergone coronary artery graft surgery and who required vasodilator therapy for postoperative hypertension were given infusions of either alfentanil or morphine together with bolus doses of midazolam for sedation and analgesia while ventilation was controlled artificially. Sodium nitroprusside (SNP) was administered to both groups using a computer-controlled closed loop system which adjusted the infusion rate to maintain a preset target arterial pressure. Target pressure ± 5, 10, 15 and 20 mm Hg was maintained longer in the group receiving alfentanil. This group also required less SNP per hour. No difference was noted between the groups in the time taken to regain spontaneous ventilation and to extubation of the trachea, although the alfentanil group tended to be sedated more deeply during the infusion. The main advantage of alfentanil over morphine at doses used in this study was its superior ability to attenuate hypertensive responses to noxious stimuli, providing improved haemodynamic stability.

The aim of our study was to assess the sedative and analgesic properties of alfentanil, and its effects on cardiovascular stability. Morphine was used as a control.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and informed consent was obtained from each patient. Forty patients who had undergone coronary artery bypass surgery and

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required postoperative vasodilator therapy were assigned randomly to receive either alfentanil or morphine infusions after operation. All patients had ECG monitoring, direct arterial pressure monitored from the radial artery and central venous pressure recorded via a right internal jugular cannula, both in theatre and in the postoperative period in the ICU. The computer-controlled closed loop system was used to administer SNP via a second dedicated central venous cannula. The cardiac surgical staff recommended the target arterial systolic pressure to which the closed loop system was set. Thereafter, the closed loop control system maintained arterial pressure as close to this as possible by varying the rate of infusion of SNP. Heart rate, arterial pressures (systolic, diastolic and mean), SNP infusion rate and target pressure were recorded on the data disc every 1 min. This closed loop control system has been described elsewhere in greater detail [2].

Following transfer of the patient to the intensive care unit, the standard practice of omitting analgesia or sedation until neurological assessment was continued. When the patient had recovered sufficiently to move all four limbs to command, a bolus dose of midazolam 2 mg was administered. The alfentanil group received a bolus of alfentanil 1 mg and an alfentanil infusion was commenced at a rate of 0.5 $\mu g\ kg^{-1}\ min^{-1}$. The morphine group received a bolus of morphine 2 mg (3 mg if the patient's weight was more than 75 kg), and an infusion of morphine 2 mg h^{-1}. Infusion rates were adjusted by the nursing staff to a maximum of alfentanil 2.0 $\mu g\ kg^{-1}\ min^{-1}$ or morphine 6 mg h^{-1}. Additional bolus doses of alfentanil 0.5 mg or morphine 1 mg were given if further analgesia was required. Midazolam 2 mg was given if staff considered that the patient was excessively aware. A record was made of the infusion rates, and of any additional bolus doses of opioid or hypnotic agent.

A simple six-point scoring chart (table I) was used by the nursing staff to assess level of sedation every 30 min for 3 h and thereafter every 1 h until infusions were discontinued. Sedation scores of 3 and 4 were considered optimal.

TABLE I. *Sedation scoring system*

1 = Sedated, no response.
2 = Responds only to painful stimuli.
3 = Responds to verbal commands but cannot indicate awareness of surroundings.
4 = Responds to commands and rousable. Comfortable.
5 = Moderately agitated.
6 = Distressed, very restless.

Once the patient was normothermic (core temperature > 36.5 °C), haemodynamically stable and with acceptable arterial blood-gas tensions, the opioid infusions were discontinued. When the patient had recovered sufficiently, s/he was allowed to breathe spontaneously via a T-piece. If arterial blood-gas tensions were satisfactory and the patient sufficiently awake, extubation was performed. Times from stopping the infusion to recovery of spontaneous ventilation and extubation of the trachea were recorded. If any further analgesia were required, papaveretum was administered i.m.

Later analysis of the arterial pressures recorded on the data disc allowed calculation of the time spent by each patient outside the target pressure ± 5, 10, 15 and 20 mm Hg. The average SNP infusion rate was also calculated.

Data from the two groups were compared using the Mann–Whitney *U* test. Statistical significance was deemed present if $P < 0.05$.

RESULTS

There was no difference between the two groups in age, sex distribution, weight or time spent on cardiopulmonary bypass. Anaesthetic regimens were not standardized, but differences between the agents used in each of the groups were not significant (table II).

There were no differences in the duration of opioid infusions or in the number of alterations in infusion rate (table III). However, the alfentanil group required significantly less additional bolus doses of opioid. In addition, less midazolam was required in the alfentanil group, although this did not achieve statistical significance.

One patient in the alfentanil group did not require arterial pressure control once the opioid infusion was commenced. Of the remaining patients, when under computer control those in the alfentanil group had arterial pressures either above the target value plus 5, 10, 15 and 20 mm Hg (fig. 1, table IV) or below the target value minus 5, 10, 15 and 20 mm Hg (fig. 2, table IV) for significantly shorter periods than those in the morphine group. In addition, the average hourly infusion rate of SNP was significantly less in the alfentanil group.

TABLE II. *Demographic data (median (range))*

	Alfentanil ($n = 20$)	Morphine ($n = 20$)
Male/Female	18/2	17/3
Age (yr)	57 (46–67)	56 (46–66)
Weight (kg)	79.4 (62–90)	80 (53.5–90)
Bypass time (min)	85 (30–120)	80 (30–140)
Anaesthetic agents		
Midazolam (mg)	20 (15–40) ($n = 18$)	20 (10–35) ($n = 20$)
Morphine (mg)	47.5 (10–100) ($n = 14$)	50 (20–100) ($n = 14$)
Fentanyl (μg)	1000 (250–1300) ($n = 9$)	950 (250–1400) ($n = 12$)

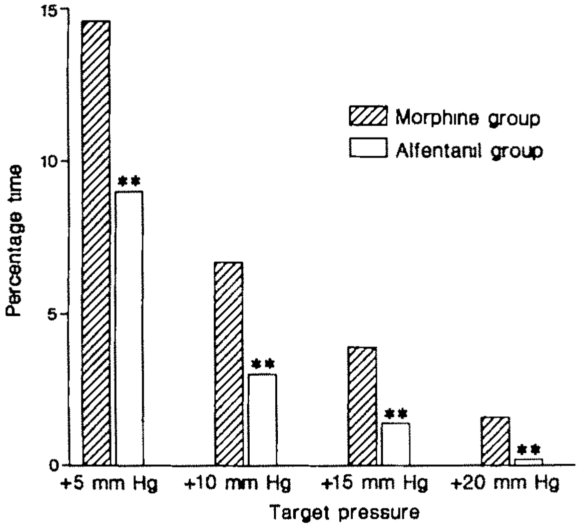

FIG. 1. Percentage of total time spent at 5, 10, 15 and 20 mm Hg above target pressure. Significant differences: $^{**}P < 0.01$.

TABLE III. *Details of infusions (median (range)).* $^{**}P < 0.01$

	Alfentanil ($n = 20$)		Morphine ($n = 20$)
Time spent on infusion (min)	232 (120–720)		300 (105–720)
No. of alterations in opioid infusion rate	1 (0–3)		1 (0–2)
Additional bolus doses			
Opioid	0 (0–5)	**	2 (0–14)
Midazolam	0.5 (0–6)		2 (0–8)

Quality of sedation while the patients received opioid infusions is shown in figure 3. Although the group receiving alfentanil appeared to spend a greater percentage of time more heavily sedated (categories 1–3), there were no statistically significant differences between the two groups at each level of sedation.

The time to recovery of spontaneous ventilation and to extubation of the trachea is shown in table V. No differences were noted between the groups.

DISCUSSION

The provision of appropriate sedation in an intensive care unit has always been difficult. The ideal agent would produce sedation and analgesia with no adverse cardiovascular effects and have a short elimination half-life with predictable but minimal accumulation when given by repeated doses or continuous infusion [6]. No single drug provides all of these properties, although propofol may approach the ideal [7]. It is common policy for an opioid infusion to be given with bolus

TABLE IV. *Percentage time (median (range)) spent outside target arterial pressure ranges while requiring arterial pressure control. Significant differences:* $^{*}P < 0.05$; $^{**}P < 0.01$

	Alfentanil ($n = 19$)		Morphine ($n = 20$)
Greater than target pressure			
+5 mm Hg	9.0 (0–17.3)	**	14.6 (6.5–31.9)
+10 mm Hg	3.0 (0–9.6)	**	6.7 (2.9–19.4)
+15 mm Hg	1.4 (0–5.7)	**	3.9 (1.9–18.1)
+20 mm Hg	0 (0–3.8)	**	1.6 (0–10.8)
Less than target pressure			
−5 mm Hg	22.2 (5.5–50.9)	**	31.9 (19.2–47.9)
−10 mm Hg	9.3 (1.2–26.3)	**	15.2 (3.8–23.6)
−15 mm Hg	4.2 (1.1–9.7)	**	7.6 (0.8–16.7)
−20 mm Hg	0 (0–2.3)	*	0.8 (0–15.3)
Average hourly SNP infusion rate (ml h^{-1})	3.2 (1–48)	**	9.2 (1–29.1)

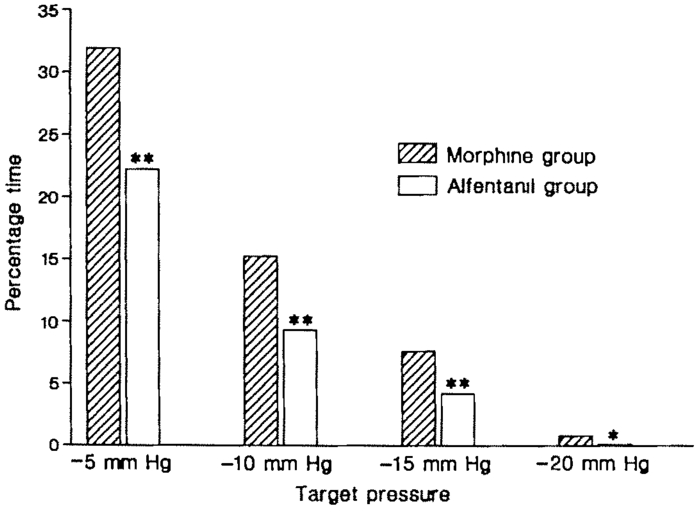

FIG. 2. Percentage of total time spent at 5, 10, 15 and 20 mm Hg below the target pressure. Significant differences: $*P < 0.05$; $**P < 0.01$.

TABLE V. *Recovery data (median (range))*

	Alfentanil ($n = 20$)	Morphine ($n = 20$)
Time to spontaneous ventilation (min)	67.5 (0–585)	60 (10–660)
Time to extubation of trachea (min)	162.5 (35–720)	192 (90–720)

administration of a benzodiazepine [8], combining continuous analgesia with a variable degree of sedation. Morphine remains the mainstay of intensive care analgesia, although its effects (or the effects of its active metabolites) may be prolonged in patients with renal impairment [9]. Alfentanil has been studied recently as being more appropriate, with its shorter half-life and its lack

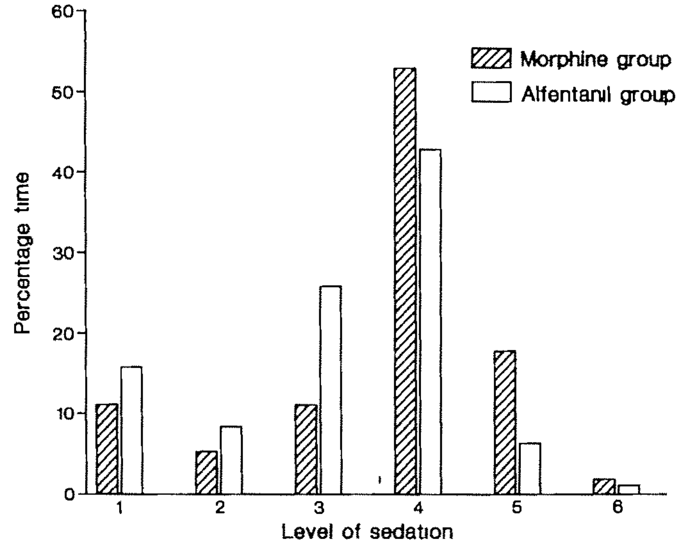

FIG. 3. Proportion of total time spent at each sedation level.

of cardiovascular effects [10]. As its use is commonly associated with respiratory depression, alfentanil may be of most value for patients whose ventilation is controlled [11, 12].

It is common policy to provide elective IPPV for patients who have undergone cardiopulmonary bypass. These patients differ from those in general intensive care units in that they are generally more fit (with the exception of cardiac pathology) and rarely have significant renal or hepatic disease, hence drug elimination is less of a problem. For these reasons, studies of sedation are often undertaken in this group [4, 5, 7]. Agents that cause excessive or prolonged sedation should be avoided if possible, because these patients are usually transferred from the ICU the day after operation. Following coronary artery surgery, it is particularly important to treat hypertension, a complication which occurs in approximately 30% of patients, and which can lead to increased haemorrhage and myocardial oxygen demand [13]. This trial was directed specifically to the group of patients who required antihypertensive therapy.

The trial was designed with two objectives. The first was to examine the effect of two sedation techniques on cardiovascular responses. Even in the best managed intensive care unit there are episodes of relatively inadequate sedation, particularly during positioning for radiography or when performing tracheal suction. This may be reflected by a period of hypertension. Under such circumstances, the closed loop control system compensates by increasing the rate of infusion. However, for a short period arterial pressure increases from the target pressure. As the closed loop control system records arterial pressure every 1 min, the time spent in various pressure bands can be calculated, hence quantifying the duration and severity of hypertensive episodes. Use of the system demonstrated a significant difference in cardiovascular stability between the two sedation groups, suggesting that the arterial pressure of the patients who received alfentanil did not deviate from the target value as much as those receiving morphine. This could be explained by the improved attenuation of hypertensive responses to noxious or other stimuli in the alfentanil group.

The second objective of the study was to assess the sedative and analgesic action of our dose regimen of alfentanil. While there was no significant difference between the percentage times spent by the two groups at each level of sedation, patients who received alfentanil spent a greater proportion of the time at levels 1–3 and those in the morphine group spent more time at levels 4–6. Our simple scoring system suggests that the patients in the alfentanil group tended to be more sedated than those receiving morphine. This would agree with the ease of control of arterial pressure in this group.

The increased degree of sedation in the alfentanil group would be a disadvantage if this had led to prolonged recovery times. However, we did not demonstrate any difference in rate of recovery in comparison with morphine. A very large range of recovery times in both groups is evident, and demonstrates the difficulties in making predictions on recovery from drugs with a short half-life, such as alfentanil. Prolonged recovery after alfentanil infusions has been reported by other authors [4, 14].

Patients in the morphine group required a significantly greater number of additional bolus injections. This suggests it is more difficult to control a morphine infusion to achieve a desired degree of sedation, and may be explained by the slower onset time of morphine. The short duration of action of alfentanil requires its administration by continuous infusion. However, its rapid action allowed easier control of the degree of sedation because it required less additional bolus injection. Our choice of alfentanil infusion rate was based on both previous literature [4] and our own clinical observation. Our choice of morphine infusion rate was based on what was common practice in the intensive care unit. The doses of the two opioids administered to patients in our study were similar when calculated on an mg h^{-1} basis. However, animal studies have shown that alfentanil is approximately 70 times as potent as morphine [15], which would result in a much greater attenuation of haemodynamic responses, with improved cardiovascular stability, in the alfentanil group.

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RISK OF MYOCARDIAL ISCHAEMIA DURING ANAESTHESIA IN TREATED AND UNTREATED HYPERTENSIVE PATIENTS

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SUMMARY

Hypertensive patients were monitored for myocardial ischaemia during anaesthesia and surgery with the V5 lead of a standard electrocardiograph. Myocardial ischaemia was detected in 11 of 39 untreated hypertensive patients and in four of seven receiving therapy with a diuretic, but in none of 44 receiving atenolol. Fourteen of the atenolol-treated patients were receiving the drug on a long-term basis and the remaining 30 were treated acutely only on the morning of surgery. When myocardial ischaemia was observed, it was always associated with noxious stimulation and tachycardia, but a conspicuous increase in arterial pressure was not usually present. We conclude that myocardial ischaemia is prevalent during anaesthesia in untreated hypertensive patients, and that pretreatment with atenolol, but not diuretics, provides prophylaxis.

Hypertension increases the risk of myocardial ischaemia during anaesthesia [1, 2] and antihypertensive therapy reduces that risk [3]. This study was undertaken to corroborate the studies of Prys-Roberts and his colleagues, and to determine if the type of antihypertensive therapy influences either the incidence of myocardial ischaemia or the vital signs seen during anaesthesia and surgery.

Diuretics and β-adrenoceptor antagonists are prescribed commonly for the treatment of hypertension. In this study we have compared untreated, chronically treated and acutely treated patients.

PATIENTS AND METHODS

With the approval of the Central Oxford Research Ethics Committee, 90 mildly to moderately hypertensive surgical patients were studied. Sixty-nine were not receiving antihypertensive therapy; at least three measurements of arterial pressure on the day before surgery were between 160/90 and 200/100 mm Hg. With their informed consent, 30 of these untreated hypertensive patients were allocated randomly to receive a single 50-mg tablet of atenolol by mouth 2 h before induction of anaesthesia. Patients suffering from heart block, heart failure or asthma were excluded. Fourteen other patients with a history of hypertension were receiving atenolol 50 or 100 mg per day for a prolonged period including the day of operation. Seven additional patients were receiving chronic diuretic antihypertensive therapy (chlorothiazide-3, furosemide-2, spironolactone-1, chlorthalidone-1) up to the day of operation. These chronically treated patients were receiving only one antihypertensive drug. No patient had a history of overt coronary heart disease or a preoperative electrocardiogram indicating left ventricular hypertrophy and strain or left bundle branch block.

The decision to proceed with anaesthesia and operation was left to the discretion of independent clinicians who selected an appropriate premedication and anaesthetic. Opioids, benzodiazepines and vagolytic drugs were prescribed

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frequently as premedication. Those who did not receive opioid premedication were given fentanyl during induction of anaesthesia, which was with thiopentone or etomidate; a myoneural blocker was administered to facilitate tracheal intubation. Halothane was the volatile agent used most commonly, but nitrous oxide with opioid supplementation and enflurane were also frequently administered. All patients underwent major surgery, which varied in duration, and those patients who had long procedures usually received additional opioid before emergence.

In the anaesthetic room, operating theatre and recovery area a V5 lead of the electrocardiogram was displayed continuously, and calibrated paper strip recordings were obtained during induction, tracheal intubation, the early phase of surgery, other intraoperative stressful periods, emergence, extubation of the trachea and at any time the vital signs changed significantly or myocardial ischaemia was seen on the monitor. Subsequently, these electrocardiographic recordings were interpreted by a cardiologist who was unaware of the patient's group or therapy. The diagnosis of myocardial ischaemia was based upon the appearance of new ST-segment depression of at least 1 mV with a horizontal or downsloping configuration (fig. 1). Heart rate and arterial pressure were measured and recorded every 1 min by a non-invasive Datascope Accutorr system.

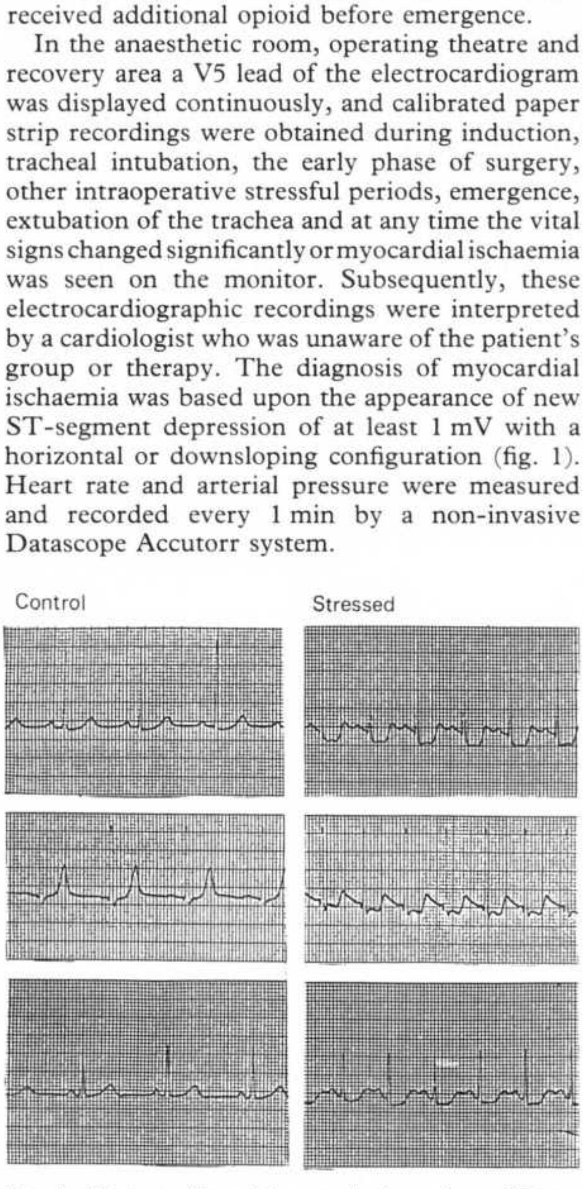

FIG. 1. Electrocardiographic records from three different patients before and during ischaemia.

Venous blood samples (5 ml) were obtained from the patients medicated with atenolol just before induction of anaesthesia and again upon entry to the recovery area. After centrifugation, the supernatant was frozen and the plasma concentration determined at a later date by gas–liquid chromatography [4]. Categorical data were evaluated by chi-square analysis, and numerical comparisons performed by analysis of variance and unpaired *t* tests which were corrected for inequalities of variance as described by Bonferroni. $P < 0.05$ was considered significant.

RESULTS

Myocardial ischaemia was detected in 11 of 39 untreated control patients, in four of seven treated with diuretics and in none receiving atenolol. Those patients who were either untreated or treated with a diuretic demonstrated significantly more myocardial ischaemia than the atenolol-medicated patients ($P < 0.001$), even though their risk factors and demographic characteristics were not significantly different.

All ischaemic episodes took place during stimulation of great intensity such as intubation of the trachea or emergence from anaesthesia. With one exception, all were self-limited and of short duration, and no patient suffered a perioperative myocardial infarct. Tachycardia was present during all of these episodes, heart rate reaching a mean (SEM) of 119 (3) beat min^{-1} at those times. Patients who did not develop myocardial ischaemia during intubation or emergence (and excluding those who received atenolol) were found to have a slower concurrent mean heart rate of only 93 (3) beat min^{-1} ($P < 0.05$). In contrast, a conspicuous increase in arterial pressure did not usually accompany the development of ischaemia. During ischaemic episodes the associated mean systolic arterial pressure was 192 (11) mm Hg, which was not significantly different from that found during tracheal intubation or emergence in patients who did not receive atenolol or develop ischaemia (179 (13) mm Hg).

Ventricular extrasystoles were observed during intubation or emergence in seven untreated patients and in two receiving diuretic therapy, But ectopic beats were not seen in patients treated with atenolol ($P < 0.001$). Episodes of bradycardia, defined as at least 1 min with heart rate of less than 45 beat min^{-1}, were noted only in patients medicated with atenolol. The incidence

TABLE I. *Measurements of arterial pressure and heart rate (mean (SEM)). Significant changes ($P < 0.05$) from measurement *on day before operation; †before induction*

	Day before operation	Before induction	Tracheal intubation	Emergence
Systolic arterial pressure (mm Hg)				
Untreated	169 (3)	161 (3)	179 (5)†	182 (6)†
Diuretic	166 (6)	173 (7)	178 (11)	191 (7)†
Chronic atenolol	158 (4)	147 (5)	171 (9)†	164 (7)†
Acute atenolol	168 (3)	135 (4)*	140 (5)	144 (6)
Diastolic arterial pressure (mm Hg)				
Untreated	89 (1)	87 (2)	98 (3)†	100 (3)†
Diuretic	85 (3)	84 (4)	94 (5)†	101 (7)†
Chronic atenolol	94 (2)	80 (4)*	99 (5)†	94 (3)†
Acute atenolol	92 (1)	80 (2)*	91 (4)†	88 (2)†
Heat rate (beat min^{-1})				
Untreated	79 (2)	78 (3)	99 (3)†	100 (2)†
Diuretic	77 (5)	86 (6)	102 (5)†	104 (7)†
Chronic atenolol	65 (3)	58 (2)	81 (2)†	79 (2)†
Acute atenolol	78 (2)	60 (2)*	72 (2)†	71 (2)†

of bradycardia was 30% in these atenolol-treated patients, and thus it occurred more frequently than in the other groups ($P < 0.001$). Hypotension, defined as a persistent systolic arterial pressure of less than 70 mm Hg, occurred on induction of anaesthesia in two untreated patients, in one receiving diuretic therapy and in four who had received atenolol. However, this apparent difference between groups was not significant. Moreover, neither hypotension nor bradycardia were associated with myocardial ischaemia.

Arterial pressure was similar in all four groups on the day before surgery. In the group receiving chronic atenolol therapy, heart rate was slower ($P < 0.05$) (table I). In the operating theatre before the induction of anaesthesia, the patients who had received either chronic or acute atenolol treatment had slower heart rates and lower arterial pressures than the others ($P < 0.05$). During tracheal intubation and emergence from anaesthesia, heart rate and arterial pressure increased in almost every patient. However, patients acutely treated with atenolol demonstrated the most attenuation of vital signs and thus the lowest peaks ($P < 0.05$); those receiving chronic atenolol therapy had slower heart rates than the untreated or diuretic-treated patients ($P < 0.05$), even though arterial pressures were not significantly different.

The therapeutic plasma concentration for atenolol varies between 200 and 5000 ng ml^{-1} [5]. The patients in this study who received acute atenolol treatment had a mean plasma concentration of 324 (54) ng ml^{-1} just before induction and a plasma concentration of 321 (40) ng ml^{-1} shortly after emergence. Those receiving chronic atenolol therapy had concentrations of 439 (93) and 302 (78) ng ml^{-1}, respectively.

DISCUSSION

Despite advances in recognition and therapy, hypertension remains a major cause of death and disability from coronary, cerebral and renovascular disease. Anaesthetic risk also is increased by hypertension [6], as these patients are more likely to exhibit substantial fluctuations in haemodynamic state [1, 3, 7], myocardial ischaemia [1, 2, 7] and perioperative myocardial reinfarction [8] than normotensive control patients. Chronic antihypertensive therapy tends to stabilize arterial pressure and to decrease the incidence of ischaemia during anaesthesia [1, 3, 7]. However, as the present study shows, not all therapy is equally protective.

β-Adrenoceptor antagonists competitively inhibit sympathetic adrenergic overactivity and thereby suppress increases in arterial pressure, heart rate and myocardial oxygen consumption. Blunting the hyperdynamic response to stress during anaesthesia is responsible for the reduced incidence of myocardial ischaemia and arrhythmias [3]. Various beta-blockers and different routes of administration have proved effective in the operating room. Atenolol has been used to attenuate arrhythmias during fibreoptic bronchoscopy [9], but these patients were pretreated for 3 days before surgery. In this study prophylaxis agonist both ischaemia and arrhythmia was achieved equally well with either chronic atenolol therapy or a single dose of the smallest commercially available tablet, taken 2 h before surgery.

Atenolol is absorbed rapidly following oral administration and the plasma concentration is sustained for a minimum of 12 h thereafter [10]. When ambulatory patients receive beta-blockers for the first time, bradycardia and postural hypotension are not uncommon [11]; we believe this observation provides a possible explanation for why the acutely pretreated patients in this study had lower arterial pressures and slower heart rates during anaesthesia than those receiving chronic atenolol therapy.

All beta-blockers slow heart rate, but atropine 1 mg i.v. produced an increase in the heart rate of our patients. Atenolol is a cardioselective or beta-1 adrenoceptor antagonist, but its specificity diminishes as the dose increases [12]. Although not statistically more prevalent in the atenolol-treated groups in this study, hypotension may well occur as a result of the unopposed beta-2 vasodilator action of the drug, its inhibition of plasma renin activity, negative inotropic effect and additive interaction with potent anaesthetics. Nevertheless, the hypertensive patient behaves in a more labile fashion during anaesthesia, and it is not possible from our data to determine if atenolol contributed to any of the observed hypotension.

Diuretics are the most commonly prescribed antihypertensive therapy. However, recent reports indicate that hypertensive patients controlled with diuretics may show a higher incidence of both myocardial infarction and sudden death than those treated with other forms of therapy [13–16]. Although the group of patients in this study who were receiving diuretic antihypertensive therapy was small, it appears that these drugs provided little if any protection against stress-induced myocardial ischaemia. Moreover, arterial pressure and heart rate during anaesthesia were not different from those seen in the untreated control group. We postulate that the failure of the diuretics to provide protection may be related to two actions: first, diuretics decrease blood volume [17] and increase circulating concentrations of vasoactive substances [18–21], leading to increased cardiovascular lability; second, many diuretics cause greater extracellular than intracellular depletion of potassium [22] and thus increase the tendency to ventricular ectopic activity [23, 24].

Another form of antihypertensive therapy which has been advocated recently for perioperative use is clonidine by mouth [25, 26]. This drug acts centrally to reduce sympathetic outflow and thereby decreases plasma catecholamine and aldosterone concentrations and renin activity.

The principal conclusions to be drawn from this study are:

(1) Untreated hypertensive patients are at considerable risk of developing myocardial ischaemia during anaesthesia.

(2) Ischaemia occurs during stressful stimulation and is accompanied by tachycardia.

(3) Antihypertensive therapy with diuretics does not protect anaesthetized patients against the risk of ischaemia.

(4) β-Adrenergic blockade with atenolol appears to protect, whether taken before operation on a chronic basis or given acutely as a single, small, oral dose on the day of operation.

(5) Beta-blocker prophylaxis produces a slower heart rate during anaesthesia and operation and may induce hypotension.

(6) If beta-blocker prophylaxis is used, anaesthesia and surgery can probably be undertaken with safety in the mildly or moderately hypertensive patient.

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ADVERSE REACTIONS TO ATRACURIUM AND ALCURONIUM

A Prospective Surveillance Study

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SUMMARY

A multicentre prospective surveillance study was undertaken to compare the incidence and severity of adverse reactions attributed to atracurium and alcuronium. Clinical manifestations were used by the anaesthetist to diagnose an adverse reaction (a cutaneous reaction, a greater than 20% change in arterial pressure or heart rate, and bronchospasm). Of the 1856 patients receiving atracurium, 10.1% had adverse reactions compared with 17.9% of the 1425 patients receiving alcuronium ($P < 0.001$)*. There were no longterm sequelae. The atracurium group had a markedly lower incidence of hypotension (3.4% v. 13.7%;* $P < 0.0001$)*, but a higher incidence of cutaneous reactions (4.6% v. 2.3%;* $P < 0.005$) *which were not associated with other adverse reactions. There was a low incidence of bronchospasm in both groups (0.2% v. 0.1%).*

During its preliminary evaluation in man it was found that atracurium caused mild systemic arterial hypotension and tachycardia at the upper end of its clinical dose range (0.6 mg kg^{-1}) as a result of the release of histamine [1]. However, lower doses of atracurium have, on occasions, been associated with hypotension [2] and a high incidence of cutaneous reactions [3]. It is difficult to assess the clinical significance of such reports because of the large interpatient variation in histamine directly released by an administered drug [4, 5]. A multicentre prospective surveillance study was undertaken to investigate the safety of atracurium in clinical practice by determining the incidence and severity of adverse reactions. A control group received alcuronium, which has been reported to be safe, with minimal potential for releasing histamine, and to have few cardiovascular effects in clinical doses [6, 7].

PATIENTS AND METHODS

The study was approved by the Medical Ethics Committees of the participating institutions. In-patients who were undergoing surgical procedures requiring the use of a neuromuscular blocking drug were randomly allocated to receive either atracurium or alcuronium. Because the Federal Department of Health (Australia) required that surveillance data be collected on all patients who received atracurium, the atracurium group included patients with significant renal disease in whom the anaesthetist thought that atracurium was specifically indicated, and patients who gave informed consent for its administration in approved studies (125 patients). In the approved studies, the patients received an initial bolus dose of atracurium 0.5–0.6 mg kg^{-1}, with further atracurium administered either by small incremental doses or by continuous infusion.

The anaesthetist who administered the neuromuscular blocker monitored the patient for adverse reactions, defined as any general or local skin reaction, a greater than 20% increase or

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decrease in arterial pressure or heart rate, bronchospasm or any other unexpected, undesired reaction which the responsible anaesthetist considered was possibly or probably caused by the administration of the neuromuscular blocking drug. A data form was provided on which details of the patient, anaesthetic and adverse reaction were recorded.

All severe life-threatening adverse reactions were investigated. The probable agent and mechanism were determined by measurement of serial serum complement, IgE and serum histamine concentrations taken from the time of the reaction, and intradermal skin testing at 6 weeks.

Nominal and ordinal data were tabulated and any differences between the groups tested for statistical significance ($P < 0.05$) by the Chi square test with Yates' correction for small groups where appropriate, or the Mann–Whitney *U* test (two-tailed). Interval data were tested using Student's *t* test, Mann–Whitney *U* test or the Kruskal–Wallis one-way analysis of variance, or a combination of these.

RESULTS

Of the 3281 patients entered into the study, 1856 received atracurium and 1425 alcuronium. The demographic data for the two groups of patients are summarized in table I. The atracurium group comprised more patients taking medication for the treatment of hypertension ($P < 0.05$) and more patients in ASA classes III and IV ($P < 0.0001$). These differences may be attributable to the higher incidence of patients with renal failure in the atracurium group (3.4% *v.* 1.1%). The ASA classifications of the 125 patients who received atracurium in other approved studies were: class I 31 patients, class II 60 patients and class III 34 patients.

The initial doses of atracurium and alcuronium were 0.47 (SD 0.11) mg kg^{-1} and 0.25 (0.09) mg kg^{-1}, respectively. Table II summarizes the initial dose of neuromuscular blocking drug for each group as multiples of the dose found to produce 95% twitch inhibition during barbiturate–narcotic–nitrous oxide anaesthesia (ED_{95}).

Adverse reactions were considered by the responsible anaesthetist to have possibly or probably been caused by the non-depolarizing neuromuscular blocking drug in 187 of the 1856 patients administered atracurium (10.1%), and in 255 of the 1425 patients receiving alcuronium (17.9%).

TABLE I. *Demographic data of patients. Nominal and ordinal data are presented as total number (percentage of the number of patients administered that agent)*

	Atracurium	Alcuronium
Number	1845	1420
Age (yr) (mean (SD))	45.6 (20.9)	43.6 (20.2)
Weight (kg) (mean (SD))	67.1 (16.2)	68.1 (15.9)
Sex		
Male	829 (46.4%)	666 (48.3%)
Female	958 (53.6%)	714 (51.7%)
ASA classification		
I	913 (50.4%)	812 (59.1%)
II	497 (27.5%)	399 (29.0%)
III	340 (18.8%)	153 (11.1%)
IV	57 (3.1%)	9 (0.7%)
V	3 (0.2%)	2 (0.1%)
Emergency cases	212 (11.4%)	160 (11.2%)
Atopy	266 (14.3%)	202 (14.2%)
Renal failure	64 (3.4%)	15 (1.1%)
Medications		
Antihypertensives	265 (14.3%)	161 (11.3%)
Bronchodilators	100 (5.4%)	64 (4.5%)

TABLE II. *Initial dose of neuromuscular blocking drug as multiples of ED_{95} dose. The ED_{95} of atracurium is 0.2 mg kg^{-1} [8] and of alcuronium 0.28 mg kg^{-1} [9] under barbiturate–narcotic–nitrous oxide anaesthesia. Difference in the dose distribution statistically significant* ($P < 0.00005$)

Dose (×ED_{95} mg kg^{-1})	Atracurium (%)	Alcuronium (%)
0–0.50	0.1	2.5
0.51–1.00	0.9	75.3
1.01–2.00	22.0	22.1
2.01–3.00	67.8	0
> 3.01	9.3	0.1

The type and incidence of the adverse reactions, with the statistical significance of any difference between the groups, are summarized in table III. There were no long term sequelae reported following these adverse reactions and no other adverse reactions were reported.

The most clinically significant finding was the marked difference in the incidence of systemic arterial hypotension between the atracurium and the alcuronium groups. Moderate hypotension (20–50% decrease in baseline arterial pressure) was noted in 63 patients administered atracurium (3.4%), compared with 184 patients given alcuronium (12.9%). This difference was also noted with severe hypotension (a greater than 50% decrease in arterial pressure) being reported in one patient administered atracurium (0.1%),

TABLE III. *Adverse reactions which were considered possibly or probably caused by the administration of atracurium or alcuronium. An adverse reaction for a cardiovascular variable was defined as greater than a 20% change from baseline. Data presented as the total number of patients having an adverse reaction (percentage of the total number of patients administered that drug). Statistical significance taken as* P < *0.05*

Adverse reaction	Atracurium	Alcuronium	*P*
Overall	187 (10.1%)	255 (17.9%)	< 0.0001
Skin reaction			
Localized	46 (2.5%)	17 ((1.2%)	< 0.05
Generalized	39 (2.1%)	15 (1.1%)	<0.05
Hypotension	64 (3.4%)	195 (13.7%)	< 0.001
Hypertension	20 (1.1%)	8 (0.6%)	ns
Bradycardia	11 (0.6%)	2 (0.1%)	ns
Tachycardia	35 (1.9%)	54 (3.8%)	< 0.005
Bronchospasm	4 (0.2%)	2 (0.1%)	ns

TABLE IV. *Statistical correlations between adverse reactions*

Blocking drug	Reactions	*P*
Atracurium	Hypotension–Tachycardia	= 0.0001
	Hypertension–Tachycardia	< 0.0001
	Bronchospasm–Tachycardia	< 0.0001
Alcuronium	Hypotension–Tachycardia	< 0.0001
	Hypertension–Tachycardia	< 0.0001
	Hypertension–Bronchospasm	< 0.0001
	Bronchospasm–General skin reaction	< 0.01
	Tachycardia–General skin reaction	= 0.0001

compared with 11 patients receiving alcuronium (0.8%).

A number of factors were identified which were associated with an increased incidence of hypotension: age greater than 60 yr; ASA class II, III; emergency; current medication: antihypertensives. Patients belonging to ASA classes II and III had a higher incidence of hypotension compared with patients in ASA class I, there being insufficient patient numbers in ASA classes IV and V for statistical analysis. An atopic tendency (patients with a history of hayfever, eczema or asthma), a history of drug allergy, the initial dose of drug and its site and rate of administration (less than or greater than 10 s) had no effect on the incidence or severity of adverse reactions.

The atracurium group had a higher incidence of cutaneous reactions which were not associated with other manifestations of systemic histamine release (table IV). Tachycardia was the most frequent clinical symptom associated with other adverse reactions.

The adverse reactions occurred within 1–30 min of administration, with a median time of 2–3 min, depending on the adverse reaction. The adverse reaction occurring 30 min after the administration of the myoneural blocker was a local skin reaction.

One patient in the study had a severe life-threatening reaction. During the anaesthetic the patient developed severe bronchospasm and profound hypotension which appeared to be temporally related to the administration of dextran 40 (Rheomacrodex). The reaction occurred 90 min after the induction of anaesthesia and 25 min after the administration of an incremental dose of atracurium. Subsequent immunological investigation excluded atracurium as the causative agent—which was presumed to be dextran 40 (Rheomacrodex).

DISCUSSION

Clinical manifestations alone are unreliable in providing a diagnosis of an adverse reaction which occurs following the administration of a neuromuscular blocking drug. During general anaesthesia other agents, including i.v. induction agents and volatile anaesthetic agents, are administered in conjunction with neuromuscular blocking drugs and manipulations such as laryngoscopy and intubation are performed. Any of these may, on occasion, be the cause of an observed adverse reaction. Hence caution should be used in analysing the data from each group in isolation. However, the randomization of patients to receive either atracurium or alcuronium allowed any significant difference in the incidence of an adverse reaction between the two groups to be attributed to the differing properties of the neuromuscular blocker. The inclusion of non-randomized patients in the atracurium group does not necessarily invalidate the findings. The patients receiving atracurium in other approved studies (6.7% of reported administrations) had similar characteristics and drug dosage compared with the other patients in this study.

The most important finding of the study is the difference in the incidence of systemic arterial hypotension between the atracurium and the alcuronium groups. This is not the result of any bias which may have been introduced by the slight difference between the groups in patient characteristics or dose of neuromuscular blocking drug. The atracurium group had a higher percentage of patients with characteristics which may predispose to hypotension (table IV) and received comparatively larger initial doses (table II).

The occasional episodes of hypotension which were reported with atracurium are probably attributable, at least partially, to the release of histamine. Histamine, and perhaps other vasoactive substances, are released by a direct pharmacological mechanism following the administration of competitive neuromuscular blockers [10]. Hypotension is a classical sign of a systemic histamine reaction. The degree of hypotension following the administration of atracurium correlates with the increase in plasma histamine concentration [1]. The low incidence of hypotension, particularly severe hypotension, in the atracurium group suggests that the overall potential for atracurium to cause a clinically significant systemic histamine reaction is small when using clinical doses. In contrast, the high incidence of hypotension in the alcuronium group suggests that the cardiovascular effects of alcuronium are more significant than previously reported. The mechanism of this hypotensive effect was not determined in this study, but may be a ganglion blocking action as well as histamine release [6].

Systemic histamine release in response to administered atracurium, although having a low incidence, can assume clinical importance. Important factors which may influence the amount of histamine released by a drug are the patient's individual sensitivity, and the size and rate of administration of the bolus dose [10]. As the size of the bolus dose increases, there is a greater likelihood of a systemic histamine response [11]. Very slow administration of large bolus doses of atracurium (0.6 mg kg^{-1} over 75 s) can minimize the release of histamine and prevent associated haemodynamic responses [12]. It has been suggested that even small differences in the rate of administration of the drug can lead to significant changes in the likelihood of generating clinically significant histamine release [10]. However, in this study, the incidence of hypotension was not changed by small differences in the rate of administration or variations of the dose of atracurium within the normal clinical range (0.2–0.6 mg kg^{-1}). It appears for atracurium that the predominant factor in systemic histamine release is the patient's individual sensitivity. This, unfortunately, cannot be accurately predicted. However, several patients were identified in whom the response to histamine was probably potentiated (table IV). In these and other patients very slow administration of atracurium, over 1 min or longer, should minimize any hypotension or other systemic histamine-mediated effects. The hypotensive effect of alcuronium also cannot be predicted, but slow administration may not decrease the incidence or severity. The degree of hypotension resulting from ganglion blockade is not affected by the rate of drug administration. Alcuronium, therefore, should be used with caution in patients who are at risk from hypotension, such as those with ischaemic heart disease.

There was a low incidence of bronchospasm in both the atracurium and the alcuronium groups. It has been suggested that atracurium may cause bronchospasm by a version of aggregate anaphylaxis [13]. The formation of aggregates of precipitated drugs, particularly atracurium and thiopentone, can cause reddening along the site of the injection vein, but may initiate acute, life-threatening bronchospasm if the precipitate is of appropriate size and concentration. Thiopentone was almost universally used to induce anaesthesia in the participating institutions during the period of the study. However, no patient in this study with a cutaneous reaction following the administration of atracurium developed bronchospasm. This may be attributable to the common practice of using a fast-flowing i.v. infusion for induction of anaesthesia in the participating institutions, thereby minimizing any mixing and precipitation of induction agent with atracurium.

The administration of atracurium was associated with a higher incidence of local and generalized skin reactions compared with alcuronium, although the incidence was not as high as previously reported [3]. The cutaneous responses to atracurium were not associated with other manifestations of systemic histamine release and have previously been shown not to correlate with changes in plasma histamine concentration [14]. This suggests that these reactions are predominantly skin histamine release [13] and, hence, are not indicative of a tendency to cause systemic histamine reactions as occurs with other neuromuscular blockers such as tubocurarine [15].

We conclude that, in normal clinical doses, atracurium is safe, with a lower incidence of adverse reactions, notably hypotension when compared with alcuronium.

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SELF-TUNING, MICROPROCESSOR-BASED CLOSED-LOOP CONTROL OF ATRACURIUM-INDUCED NEUROMUSCULAR BLOCKADE

P. C. UYS, D. F. MORRELL, H. S. BRADLOW AND L. B. RAMETTI

SUMMARY

A self-tuning, closed-loop computerized system was used to maintain atracurium-induced neuromuscular blockade in patients undergoing routine lower abdominal gynaecological surgery. The controller is based on a unique algorithm which utilizes a bi-exponential model wherein two of the variables are estimated on-line. This enables the system to optimize the sizes of subsequent bolus doses according to patient sensitivity. In this study an initial bolus of 0.3 mg kg^{-1} *was given in a trade-off aimed at achieving earlier intubating conditions rather than taking control of relaxation* ab initio *and obtaining the pre-programmed setpoint of 15% single twitch response (STR) without overshoot. This was successful in all of the 11 patients studied, the mean time from injecting the bolus to intubation being 2.47 (SD 0.95) min and the drug maintenance requirement being 0.34 (0.07)mg* kg^{-1} h^{-1}*. This provided a mean value of 10.26% STR with minimal oscillation about the setpoint (average standard deviation = 4.31 (2.53)) for up to 147 min.*

Blockade of neuromuscular transmission has a well defined endpoint which can be relatively easily measured in the clinical setting. Consequently, feedback control can be exercised by a system which can measure activity at the neuromuscular junction, calculate the dose of drug necessary to achieve a predetermined degree of block and then inject this dose i.v. We have developed and previously described such a closed-loop system which was used initially to control neuromuscular blockade induced with tubocurarine [1]. The hallmark of our system is that it is self-tuning. By taking into account each patient's response to the drug, subsequent dosing is thus tailored individually to patient variability and any other factors affecting neuromuscular function. In this way a more precise pharmacodynamic response with the most economical use of drug can be obtained, while achieving and maintaining paralysis appropriate to prevailing demands.

The system was adapted for atracurium, and an initial assessment was performed to determine and test population parameters for atracurium [2]. We now present the results of its application in gynaecological surgery in which neuromuscular blockade was induced with a 0.3-mg kg^{-1} bolus. This trade-off was aimed at rapidly achieving a single twitch response (STR) of 15% (85% blockade) to enable early tracheal intubation, but carries the penalty of overshoot well beyond the 15% setpoint.

PATIENTS, MATERIALS AND METHODS

The Control System

The working system (fig. 1) consists of the nerve stimulator, force transducer, microprocessor controller, syringe pump and a chart recorder. Inputs to the controller are from the force transducer and keyboard, and outputs are to an alphanumeric display, cassette tapedrive for data logging and off-line analysis, the recorder, and the syringe pump driver. A general overview of the elements is given below; the reader will be referred to previous work for the considerable theoretical background and practical detail.

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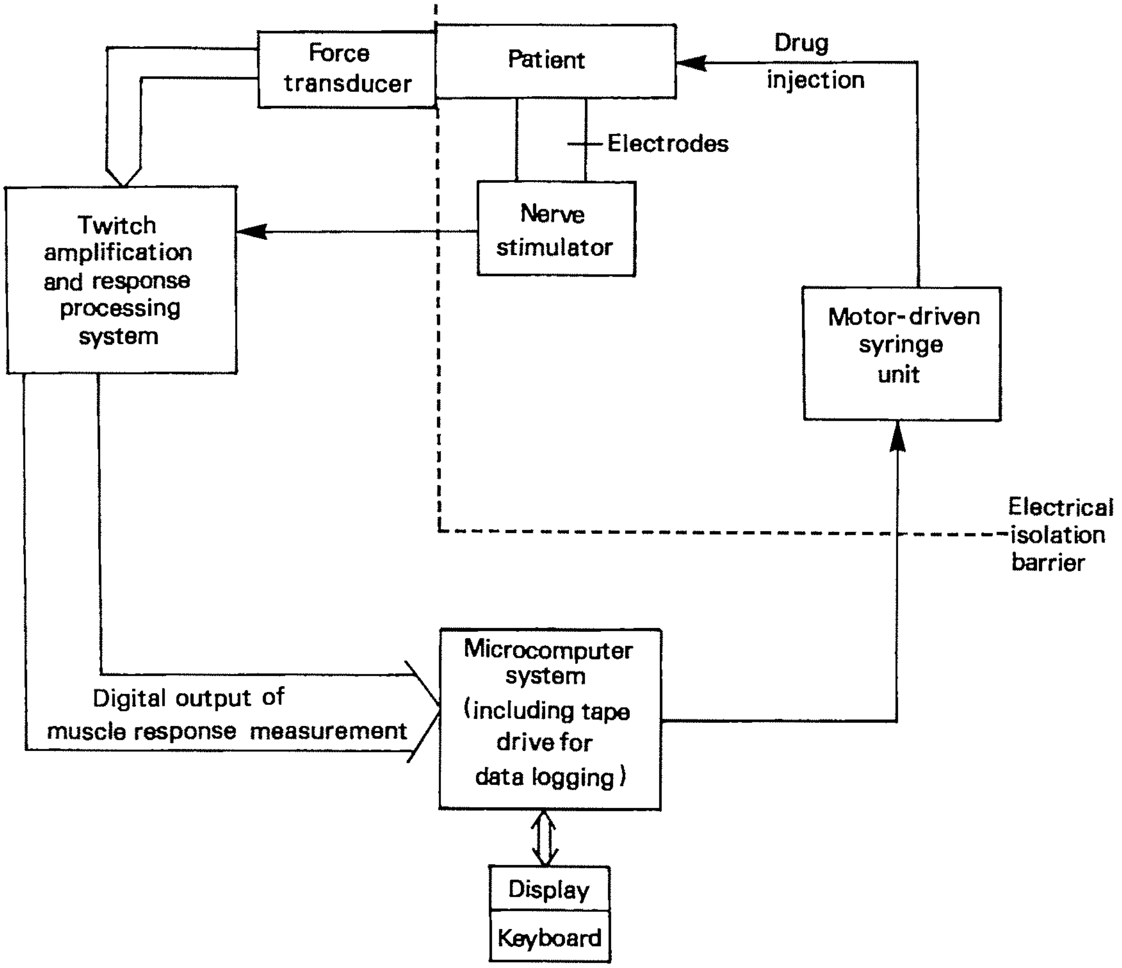
Force transducer
Patient
Drug injection
Electrodes
Twitch amplification and response processing system
Nerve stimulator
Motor-driven syringe unit
Electrical isolation barrier
Microcomputer system (including tape drive for data logging)
Digital output of muscle response measurement
Display
Keyboard

FIG. 1. Block diagram of the controller and response measurement system.

The algorithm

The algorithm is aimed at achieving and maintaining a selectable setpoint of twitch depression. It is based on a dose–response model described previously [1, 3, 4], and which can be summarized as follows:

The model is bi-compartmental, the peripheral compartment being the site of action of the drug. It is important to note that this model does not necessarily have any relation to traditional pharmacokinetic models based on plasma concentrations [5]. It is described by a single bolus response of the concentration in the "effect" compartment given by:

$$x(t) = A\{\exp[-\alpha(t-\theta)]-\exp[-\beta(t-\theta)]\}U$$

were $x(t)$ is the time dependent concentration of the drug in the effect compartment, α and β are the time constants of the model, θ is a dead time, A is the "sensitivity" of the response, and U is the size of the bolus dose.

Since dose schedules rather different from a single bolus are used, the above equation is converted by straightforward algebraic manipulation to an input–output relationship in the discrete- or sample-time domain given by:

$$x(k) = Gz^{-r}U(k)/[(1-P_1z^{-1})(1-P_2z^{-1})]$$

where k is the sample number, z^{-1} is the discrete time backward shift operator, G is the gain given by $P(e^{-\alpha\tau}-e^{-\beta\tau})$ where τ is the sampling period, $U(k)$ is the bolus input at the kth sampling instant, and P_1 and P_2 are the poles of the model given by $P_1 = e^{-\alpha\tau}$ and $P_2 = e^{-\beta\tau}$.

The pharmacodynamic relationship between the effect and the concentration in the effect compartment is obtained by using the "logistic" relationship:

$$T(k) = 1/[1 + \exp\{y(k) + B_T\}]$$

where $T(k)$ is the twitch response at the sampling instant and B_T is the variable which regulates the sigmoidal shape of the pharmacodynamic relationship.

The variables G and B_T are estimated on-line by an expanding memory, steepest-descent, nonlinear least-squares algorithm and, following previous findings that these estimates converged within 200 sampling periods, their continuous re-estimation is terminated and they remain fixed after this period.

P_1 and P_2 were not estimated on-line as simulation studies [1] indicated that little improvement could be achieved over choosing population constants obtained in this particular application from previous work on controlled atracurium-induced neuromuscular blockade [2].

The model and the parameters obtained are used in a novel control algorithm developed for this application [1]. The controller reads the twitch response every 10 s and administers a bolus dose every 1 min during the operation from initiation to the end of the control (of course, at many 1-min instants—which we refer to below as "control instants"—the dose administered is zero). At each control instant, the controller predicts future degrees of paralysis from the doses already administered and locates the maximum by using the model described above and a linear state estimator. It then calculates by a numerical method the present dose that must be administered in order to take the maximum to the desired endpoint. It has been found that this algorithm (which caters for positive-input systems and into which category this system falls as it cannot remove drug from the body) is insensitive to the patient dead time [4] and provides excellent control performance for both the induction and the maintenance of paralysis [1].

The microprocessor [6]

The CPU board utilizes the full co-processing features of an Intel 8088 CPU and 8087 floating-point numerics processor and can, consequently, cope more than adequately with the computational load imposed by the control algorithm. There are additional cards for (i) memory, (ii) keyboard controller, (iii) serial input/output, and (iv) digital cassette tape interface equipped with an 8085 microprocessor. The fifth card was designed specifically for the unit and provides an interface for the twitch measurement and syringe driver systems.

The software [6]

The control program was written in Intel 8086/88 assembly language and runs as a single task on the native computer system without the use of any operating system. Its function is to implement the control algorithm, and requires certain keyboard-entered information on initiation (see Parameter Entry below). The software runs as a continuous loop, calling two major subroutines, one of which collects the twitch data, while the other performs the control calculation and issues commands to the syringe driver. All twitch-response and calculated control data may be logged on tape cassette for subsequent at-leisure evaluation on a Univac 11/08 mainframe computer—an option which is only necessary as a research and development tool during the refinement of the program or parameter estimation of new drugs.

Twitch data validity checks are performed by ensuring that there has been no over- or underflow in the analogue-to-digital convertor of the measurement system, that pulses in the train-of-four (TOF) are monotonically decreasing, and that pulse arrival is at an interval between 400 and 700 ms.

The measurement system [6]

Neuromuscular transmission is measured by stimulating the ulnar nerve via two Medicotest paediatric silver–silver chloride surface electrodes placed over the nerve on the volar aspect of the wrist. The stimulus consists of a supramaximal TOF pattern of pulses each always less than 200 μs in duration at 0.5-s intervals every 10 s. The outstretched hand is strapped to a specially constructed armboard on which is fixed the Perspex housing of the force displacement transducer unit, and the thumb is secured to and activates a plunger mounted in a linear precision bearing so that the load is transmitted via a cantilever to two strain gauges forming half of a Wheatstone Bridge. The system has a working range of 0–100 N and the thumb is preloaded with 100–150 g.

The syringe driver [6]

The unit consists of an opto-isolated battery-driven motor which drives the plunger of a standard 20-ml disposable syringe via a worm gear and flywheel arrangement. The flywheel has circumferential holes spaced 30° apart which allow pulses to be sent to the computer with rotation through a light beam aimed at a photocell. All atracurium boluses were administered as a 0.1 % solution in 0.9 % normal saline into a freely running i.v. infusion. The pump is capable of delivering fluid at a rate of 1 ml s^{-1} and 20 mg thus takes only 20 s to be injected, which is an order of magnitude smaller than the time constant of the drug. Individual boluses and accumulated dose are displayed by the computer, and control may be overridden by switching the driver off-line.

Parameter entry

Apart from standard entries such as the case identification header, date and patient weight, the operator needs to supply the controller with other menu-selectable items of information.

(1) The variables P_1 and P_2 for atracurium and the gains of the linear state estimator which, as mentioned, were entered as default values derived in a previous study. Under working clinical conditions these items would be automatically entered when "Atracurium" was selected from a drug menu.

(2) The size of the initial bolus—in this instance 0.3 mg kg^{-1}.

(3) The ratio which is to be controlled. The menu includes STR, being the ratio of the heights of the first twitch of the TOF before and after administration of the blocking agent, and T2 and T4 ratios, being the ratio of the height of the relevant numbered twitch to the first at any stage of blockade. In this instance STR was used and thus necessitated measuring the first twitch height under stable anaesthetized conditions before the administration of the neuromuscular blocker.

(4) The setpoint for block—in this instance 15 %. This may be altered by keyboard entry during the run.

Operation

The procedure is conveniently considered as occurring in four stages, namely the monitoring, relaxation, regulation and recovery phases.

Monitoring phase. When a stable level of anaesthesia has been achieved, the system monitors the TOF until the magnitude of all four responses has been stable for at least 30 s, thus providing baseline values.

Relaxation phase. The initial bolus of atracurium 0.3 mg kg^{-1} is injected and the system then monitors the patient's response, modifying accordingly those internal parameters which determine the calculation of subsequent doses. If setpoint is not achieved, further boluses of drug

TABLE I. *Pharmacodynamic results*

Patient	Induction–blocker time (min)	Time to setpoint (min)	Overshoot duration (min)	Regulation duration (min)	Drug for regulation (mg kg^{-1} h^{-1})	Offset during regulation	
						(% Mean)	SD
1	9	3.83	11.00	136.17	0.36	−1.29	2.24
2	10	2.00	15.17	44.83	0.48	−2.89	3.28
3	8	2.00	28.00	48.33	0.27	−1.88	3.40
4	6	1.67	29.33	42.33	0.32	−4.33	3.99
5	6	3.00	17.50	44.33	0.32	−0.57	1.27
6	3	2.67	3.00	76.33	0.41	−8.54	4.92
7	6	2.00	29.83	27.83	0.29	−8.75	4.60
8	19	1.67	37.67	0.00			
9	7	1.50	25.17	35.00	0.34	−9.09	8.49
10	5	2.17	41.00	19.67	0.22	−1.69	1.72
11	7	4.67	12.83	90.50	0.35	−8.39	9.18
Mean	7.8	2.47	22.77	51.39	0.34	−4.74	4.31
SD	4.17	0.95	11.26	35.67	0.07	3.36	2.53
Maximum	19	4.67	41.00	136.17	0.48	−9.09	9.18
Minimum	3	1.50	3.00	0.00	0.22	−0.57	1.27

Correlation coefficient (r): Time to setpoint *v.* Overshoot duration = 0.05183
Time to setpoint *v.* Drug dose for regulation = 0.06699
Overshoot duration *v.* Drug dose for regulation = −0.78184

are given under microprocessor control. This phase is further subdivided into two subphases: the time from injecting the bolus to first reaching setpoint, and the overshoot period from the time of first reaching setpoint to the time of returning to setpoint.

Regulation phase. This begins when blockade returns from overshoot to setpoint and ends when control is relinquished at the end of surgery. During this phase the system controls blockade by administering the dose calculated to maintain setpoint. Self-tuning continues for the 200-sample period, which takes approximately 35 min after initiation of control. Up till then the algorithm thus allows for modification of the size of subsequent doses according to both patient response to the previous dose(s) and deviation from setpoint, and thereafter only according to deviation from setpoint.

Recovery phase. Following manual discontinuation of control, the residual blockade is antagonized, and monitoring is continued until the T4 ratio reaches 70%.

Patients

The design of the study was approved by the hospital Ethics Committee and informed consent was obtained from all subjects. Eleven ASA Class I or II patients scheduled to undergo elective lower abdominal gynaecological surgery were selected from routine lists, the only other exclusions being any form of muscular, neuromuscular or neurological pathology, or the concomitant use of drugs known to affect neuromuscular transmission.

Anaesthetic technique

Patients were premedicated with diazepam 10 mg given by mouth 2 h before the start of surgery. Anaesthesia was induced with fentanyl 100 μg and thiopentone 3–5 mg kg^{-1}, the vocal chords and upper trachea topically anaesthetized with 4% lignocaine spray 120–160 mg, and anaesthesia subsequently maintained with 70% nitrous oxide and 0.5% halothane in oxygen. Fentanyl was given in 50-μg boluses as determined by patient response to painful stimuli during the procedure. When a stable level of anaesthesia had been achieved as determined by the control system, it then injected the initial atracurium bolus and assumed further control of neuromuscular blockade. Intubation was performed when the STR had decreased to 15%, and the lungs were ventilated to maintain normocarbia (as monitored by capnography (Datex Normocap)). Other monitoring included sphygmomanometric measurement of arterial pressure and a continuous electrocardiographic display. Residual neuromuscular block was antagonized with neostigmine 2.5 mg and glycopyrrolate 0.4 mg.

RESULTS

The mean weight of the patients was 66.82 (SD 4.9) kg and their mean age 37 (9) yr. Intubating and operating conditions as afforded by the technique were always good. Atracurium itself produced minimal but no clinically significant haemodynamic changes and, despite the fact that two of the patients had a history of mild asthma, there was no clinical evidence of increased airway resistance.

The pharmacodynamic results are set out in table I. All patients achieved setpoint with the initial bolus, the average time being 2.47 (0.95) min with a maximum of 4.67 and a minimum of 1.5 min. The overshoot duration was 22.77 (11.26) min, ranging from 3 to 41 min. The regulation phase duration averaged 51.39 (35.67) min, the longest being 136.17 min. Patient 8, who was particularly sensitive to the drug, did not recover from her overshoot for 37 min after setpoint was reached and as this coincided with the end of surgery, no regulation control was necessary.

The average dose of drug used during the regulation phase was 0.34 (0.07) mg kg^{-1} h^{-1}. This figure obviously does not include the initial bolus.

The offset during regulation is used as a measure of the pharmacodynamic control afforded by the system and is expressed as the deviation of the STR from the setpoint during the regulation phase. The values tabled are all negative, which is not surprising in view of the fact that the system is triggered before setpoint is re-achieved. The value of −4.74 (3.36)% for all patients as a group thus represents a mean STR of 10.26% once setpoint had been reached. The average standard deviation of the individual offsets was 4.31 (2.53)%, indicating a very tight degree of control around setpoint. A plot demonstrating the control of blockade in patient 10 is shown in figure 2.

The induction–blocker time in table I refers to the time between induction of anaesthesia and the injection of the initial bolus, and incorporates the

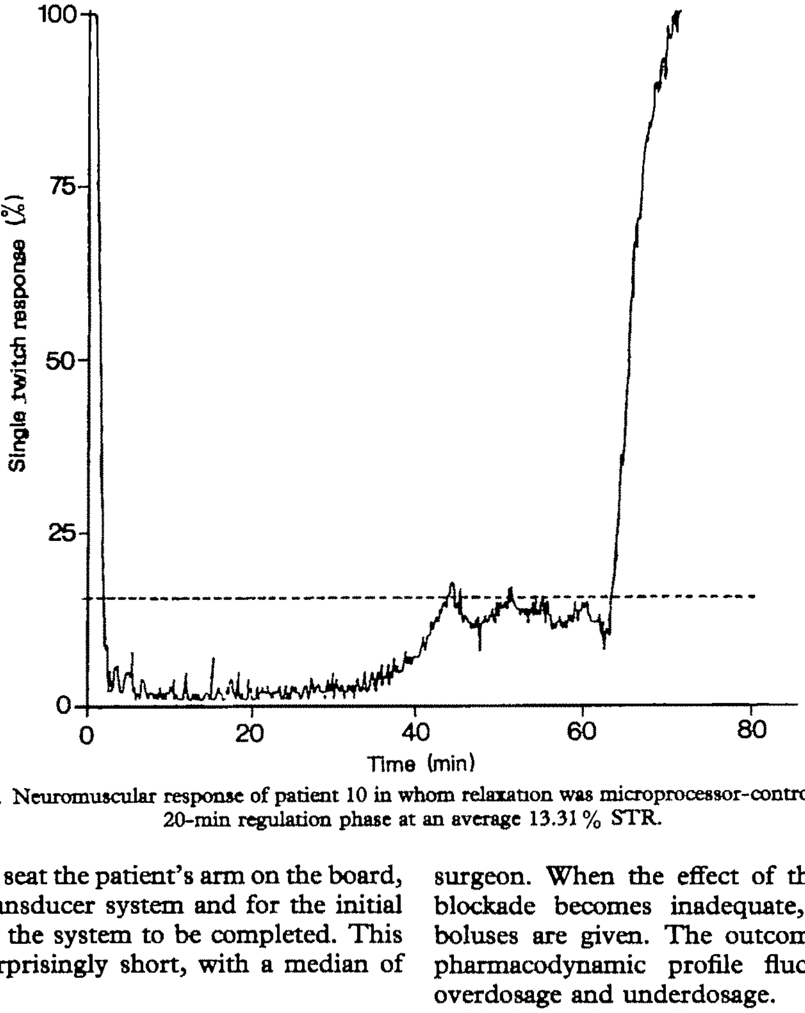

FIG. 2. Neuromuscular response of patient 10 in whom relaxation was microprocessor-controlled for a 20-min regulation phase at an average 13.31 % STR.

time needed to seat the patient's arm on the board, preload the transducer system and for the initial monitoring by the system to be completed. This period was surprisingly short, with a median of 7 min.

DISCUSSION

Control of neuromuscular blockade during clinical anaesthesia is beset by two major problems. The first is that of patient variability in response to the neuromuscular blocking drug. The exact reasons as to this differing susceptibility are incompletely understood and there is no reliable means of estimating sensitivity to the agent used before the administration of the drug. The second problem lies in the heavy-handed, traditional method of administration of neuromuscular blocking drugs. Because the anaesthetist requires rapid onset of profound blockade for intubation, the drugs are usually administered by means of a large initial bolus which produces a far greater degree of block than is required by either anaesthetist or surgeon. When the effect of this wears off and blockade becomes inadequate, further smaller boluses are given. The outcome is an unstable pharmacodynamic profile fluctuating between overdosage and underdosage.

Ideal kinetic steady-state management would involve a bolus dose to achieve the necessary plasma concentration of drug rapidly, an exponentially declining infusion to accommodate for redistribution to peripheral compartments, and a second infusion to compensate for drug elimination. Apart from the logistical problems of implementing such a technique, myoneural blockers are not amenable to pharmacodynamic control based on central compartment plasma concentrations—the concentration–response relationship is variable and inconsistent. It would thus seem more appropriate to titrate drug against effect in the time-honoured i.v. induction tradition.

Our initial investigations, using a non-linear least-squares data fitting routine and aimed at determining a suitable model for use in automated control of neuromuscular blockade with tubocurarine, indicated that a bi-exponential function sufficed [4]. In the search for a suitable controller, both a discrete time proportional-integral-derivative controller and the self-tuning controller of Clarke and Gawthorp [7] were simulated and found to give unsatisfactory results, leading us to design a self-tuning controller the algorithm of which utilized our pharmacodynamic model [1]. On-line parameter estimation and the use of the Rametti–Bradlow controller successfully overcame the problems of the dead time in patient response attributable to circulation, the non-linearity of the pharmacodynamic response resulting from initial silent receptor occupancy, the long-acting effect of non-depolarizing neuromuscular blocking agents, and the wide individual variation. Tubocurarine was chosen as a starting point because of the relative wealth of documented dynamic data available on this agent and because its long time constants provide a more stringent test.

Closed-loop systems have recently been described for the administration of pancuronium using a proportional controller [8], of vecuronium using an on-off infusion controller [9], and of atracurium by Webster and Cohen using a proportional controller [10]. Bearing in mind that our initial bolus dose was less than that used by the latter workers (0.3 *v.* 0.5 mg kg^{-1}) and that our control was only very slightly higher than theirs (10.26 *v.* 8.9 %), our maintenance infusion rate was considerably lower (0.34 *v.* 0.45 mg kg^{-1} h^{-1}).

As there is an obvious dose relationship with the time to intubation and it is generally desirable to be able to intubate as soon as possible, our trade-off in using 0.3 mg kg^{-1} as an intubating dose resulted in the clinically acceptable average time to setpoint of 2.47 min, intubation conditions being satisfactory in all patients.

In some instances there appeared to be a proportional relationship between a rapid onset of paralysis and a long duration of overshoot (patients 4, 8 and 9), but regression analysis of time to setpoint against duration of overshoot did not confirm an overall correlation. Regression analysis of time to setpoint against drug administration rate during the regulation phase also failed to expose significant correlation. Thus a rapid onset of paralysis does not necessarily mean that less drug will be required for the maintenance of blockade. This, together with the large ranges in all the pharmacodynamic parameters, underscores once again the need for individualization of dosage. There did, however, appear to be an inverse relationship between the duration of overshoot and the drug administration rate during the regulation phase.

Disadvantages of the system are largely related to the measurement system. Setting up the mechanical transducer with immobilization of the arm and preloading is time-consuming and fussy. Electromyographic techniques more resistant to movement noise would be an obvious improvement, although diathermy interference would then become a nuisance. Full screen trended on-line data display would also be an advantage.

We believe that further development aimed at a consumer market would bring inexpensive closed-loop administration of neuromuscular blocking drugs within the realm of everyday practical anaesthesia. The special advantage of attaining a stable predetermined level of neuromuscular blockade at the most economical drug consumption rate is that reversible blockade is rapidly attained, minimizing the hazard of recurarization and contributing significantly to patient safety.

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PIPECURONIUM AND PANCURONIUM: COMPARISON OF PHARMACOKINETICS AND DURATION OF ACTION†

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SUMMARY

The pharmacokinetics of pipecuronium 0.07 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} were compared in 39 ASA class I or II patients. Plasma concentrations of these agents were measured for 6 h following administration, using a sensitive and specific capillary gas chromatographic assay. Concentration v. *time data were analysed by non-linear regression and fitted to a two- or three-compartment model as appropriate. Neuromuscular blockade was assessed by measuring the mechanical evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve. Pipecuronium had a larger steady-state volume of distribution (V^{ss}) (309 (SD 103) ml kg^{-1}) and greater plasma clearance (Cl) (2.4 (0.6) ml kg^{-1} min^{-1}) than pancuronium (199 (54) ml kg^{-1} and 1.5 (0.4) ml kg^{-1} min^{-1}, respectively). The volumes of the central compartment, distribution and elimination half-lives and mean residence times were similar for both agents and within the range expected for drugs of this type. The durations of action (injection to 25% recovery of twitch tension) of pipecuronium and pancuronium were similar: 98.0 (36.1) min and 117.2 (35.8) min, respectively. We conclude that the time courses of neuromuscular blockade following pipecuronium and pancuronium are similar, despite the differences in* V^{ss} *and* Cl.

Pipecuronium bromide is a long-acting, non-depolarizing neuromuscular blocking drug which is devoid of cardiovascular effects [1]. These properties have been confirmed in both healthy patients and those with significant cardiac disease [2]. The pharmacokinetics of pipecuronium in humans were determined by Tassonyi, Szabo and Vereczkey [3], using a relatively insensitive colorimetric assay [4]. Plasma concentrations were measured for only 60 min after the injection of pipecuronium, a short sampling time that precluded accurate determination of the elimination phase. We have developed a sensitive and specific capillary gas chromatographic assay for the quaternary ammonium steroidal neuromuscular blocking agents that can measure plasma concentrations of pipecuronium for 6 h after administration of usual clinical doses [5]. We used this assay to determine the pharmacokinetics of pipecuronium in humans and, for purposes of comparison, those of its analogue, pancuronium. To compare the duration of action of these two agents, we have measured the duration of neuromuscular blockade which each produced.

METHODS AND MATERIALS

With approval from the local Committee for Human Research and written informed consent, we studied 39 patients (ASA class I or II) undergoing various surgical procedures. Patients were premedicated with diazepam 10 mg by mouth or midazolam 0.02–0.05 mg kg^{-1} i.v., as appropriate. Anaesthesia was induced with thiopentone 1–5 mg kg^{-1} i.v. and maintained with halothane 0.7–0.8% and 60–70% nitrous oxide (end-tidal concentrations) in oxygen, as determined by mass spectrometry. Oesophageal temperature was maintained at 35–37 °C and venti-

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lation was controlled to maintain end-tidal $P\text{CO}_2$ at 4–5.3 kPa.

Subcutaneous needle electrodes were placed adjacent to the ulnar nerve at the wrist; through them, a Grass S88 nerve stimulator delivered supramaximal impulses in a train-of-four (TOF) pattern at 2 Hz at intervals of 15 s. The evoked twitch tension of the adductor pollicis muscle was measured using a Gould Statham UTC3 force transducer attached to the thumb. Twitch responses were recorded on a polygraph and, following analog-to-digital conversion, on microcomputer floppy disc [6]. Measurements of the twitch responses were taken from the computer printout generated at the completion of the study. When a stable level of twitch tension was attained, the twitch response to the first stimulus in the train (T1) was taken as the control response with which all subsequent T1 responses were compared. The interval from the end of the injection of neuromuscular blocking drug until the return of T1 response to 25% of control T1 was recorded as the duration of action (Dur25).

Patients were allocated randomly to receive either pipecuronium 0.07 mg kg^{-1} or pancuronium 0.1 mg kg^{-1} as a rapid i.v. bolus. Venous blood samples were drawn before and at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 min after injection. Samples were heparinized, placed in ice, and centrifuged and acidified within 1 h. Plasma concentration (C) was calculated following single organic ion-pair extraction of the drug from acidified plasma and quantification using a sensitive and specific capillary gas chromatographic assay with nitrogen-sensitive detection [5]. This assay is specific for the pipecuronium and pancuronium parent compounds. It has a coefficient of variation 4–15% and is linear over the range 2–5000 ng ml^{-1}.

Concentration–time data were fitted to both a two-compartment ($C = Ae^{-\alpha t} + Be^{-\beta t}$), and a three-compartment ($C = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$) model by derivative-free, non-linear regression [7]. All plasma samples were assayed at the same dilution, and variance was broadly in proportion to the concentration, therefore a weighting factor of $1 \times C^{-2}$ was used. The more appropriate model in each case was determined by F test [8]. The pharmacokinetic parameters of distribution half-life $T_{\frac{1}{2}}^{\alpha}$, elimination half-life $T_{\frac{1}{2}}^{\beta}$, volume of central compartment (V_1), volume of distribution at steady rate (V^{ss}), plasma clearance (Cl) and the derived variable, mean residence time in the body (Tres), were calculated for each patient according to standard formulae [9, 10]. For both groups mean plasma decay curves were obtained by calculating the mean concentration at each time point and fitting these points to a three-compartment model (fig. 1).

Statistical comparisons were made using Student's t test for unpaired data. Differences were considered significant at $P < 0.05$.

RESULTS

Mean age and weight of the patients in the pipecuronium group (46 (SD 15) yr, 71 (13) kg) did not differ from those in the pancuronium group (41 (15) yr and 75 (15) kg, respectively).

A three-compartment model best described the pharmacokinetic data in 15 patients in the pipecuronium group and 10 patients in the pancuronium group. A two-compartment model was used in the remainder. In one patient given pancuronium, it was not possible to measure plasma concentrations beyond 240 min because of high background noise in the assay. The drug elimination phase could not be accurately determined, therefore, and the data for this patient were not included in the pharmacokinetic analysis. Compared with pancuronium, pipecuronium had a larger V^{ss} and a greater Cl. The values for $T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, V_1 and Tres were not different (table I). The durations of action (Dur25) of pipecuronium (98.0 (36.1) min) and pancuronium (117.2 (35.8) min) were not significantly different (fig. 2). Five patients in each group required antagonism of neuromuscular blockade before recovery of T1 to 25% of control.

TABLE I. *Pharmacokinetic parameters (mean (SD)) for pipecuronium and pancuronium: distribution half-life* ($T_{\frac{1}{2}}^{\alpha}$), *elimination half-life* ($T_{\frac{1}{2}}^{\beta}$), *volume of the central compartment* (V_1), *volume of distribution at steady state* (V^{ss}), *plasma clearance* (Cl) *and mean residence time in the body* (T*res*)

Pharmacokinetic parameters	Pipecuronium ($n = 20$)	Pancuronium ($n = 18$)	P
$T_{\frac{1}{2}}^{\alpha}$ (min)	16.3 (10.1)	15.6 (16.4)	ns
$T_{\frac{1}{2}}^{\beta}$ (min)	137 (68)	115 (40)	ns
V_1 (ml kg^{-1})	67.1 (30.2)	59.6 (18.5)	ns
V^{ss} (ml kg^{-1})	309 (103)	199 (54)	< 0.005
Cl (ml kg^{-1} min^{-1})	2.4 (0.6)	1.5 (0.4)	< 0.0005
Tres (min)	140 (63)	134 (26)	ns

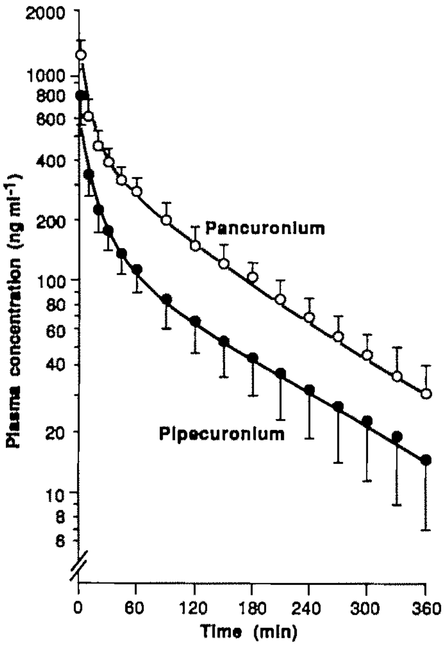

FIG. 1. Mean plasma concentration *v.* time curves for pipecuronium and pancuronium. The lines represent the fit of a three-compartment model to each set of data and are described by the equations $C = 879e^{-0.31t} + 242e^{-0.035t} + 117e^{-0.0053t}$ (pipecuronium) and $C = 948e^{-0.32t} + 356e^{-0.042t} + 340e^{-0.0045t}$ (pancuronium), where C is the plasma concentration (ng ml^{-1}) at time t.

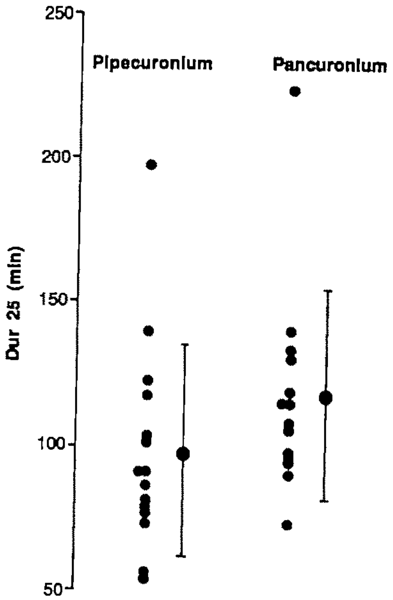

FIG. 2. Individual data points for the time from injection of pipecuronium or pancuronium until twitch tension recovery to 25 % of control (Dur25). Error bars represent the mean and standard deviation.

DISCUSSION

We have used both two- and three-compartment models to describe the concentration *v.* time data. This approach was adopted because the two-compartment model did not represent the data adequately in several patients, but there were some for whom the three-compartment model did not provide a significantly better fit than the two-compartment model [8] and, therefore, the latter was used. Mean values for the fast-distribution π half-life are not reported because this phase was not defined in cases where the two-compartment model was used. Figure 1 shows the plasma decay curves for the mean pipecuronium or pancuronium concentration at each time point and gives the tri-exponential equations which describe the models fitted to the data.

The assay we used in this study was specific for the parent compound and did not measure the metabolites of either pipecuronium or pancuronium. Previous studies of pancuronium pharmacokinetics using both specific [11] and non-specific assay techniques [12–14] have reported pharmacokinetic values similar to those which we obtained. Our findings, therefore, appear to support the contention of Cronnelly and colleagues [11], that metabolites do not contribute to the plasma concentrations of pancuronium regardless of the method of measurement.

Tassonyi, Szabo and Vereczkey [3] studied pipecuronium pharmacokinetics in humans and reported a $T_{\frac{1}{2}}^{\beta}$ of only 44 min and *Cl* of 320 ml min^{-1}. These results differ significantly from the values of 137 min and 2.4 ml kg^{-1} min^{-1}, respectively, which we derived. However, in that study [3], an insensitive colorimetric assay was used which allowed measurement of plasma concentrations of pipecuronium for only 60 min after administration. Such a short sampling time prevents accurate characterization of the elimination phase of the drug, resulting in an overestimation of the true β decay slope and an underestimation of the area under the plasma concentration *v.* time curve. We consider the values derived in our study to be more accurate estimates of the true $T_{\frac{1}{2}}^{\beta}$ and *Cl* of pipecuronium.

Our findings demonstrate that pipecuronium has a greater *Cl* and a larger V^{ss} in humans than pancuronium. In the rat, there is only minimal biliary elimination of both pipecuronium [15] and pancuronium [16]. If this pattern is the same in humans, hepatic mechanisms cannot account for the rapid clearance of pipecuronium. Because the two charged quaternary nitrogen groups are located more peripherally on the pipecuronium than on the pancuronium molecule, it is likely that there are differences in the hydrophilic and protein-binding characteristics of these two drugs. The structural differences suggest that pipecuronium is the more polar and hence the more hydrophilic molecule. This characteristic might enhance the renal elimination of pipecuronium and account for its greater clearance.

In addition, if pipecuronium were bound less to plasma protein than to pancuronium, this would explain the greater V^{ss} of pipecuronium. Pipecuronium is 32% bound to plasma protein in the rat [17], while estimates for pancuronium protein binding range from 7% to 87% [18–20]. With the evidence available, the differences in V^{ss} cannot be attributed to differences in the protein binding characteristics of the drugs.

The end result of the differences in V^{ss} and Cl is that the elimination phases for pipecuronium and pancuronium are similar. As can be seen from the mean plasma decay curves (fig. 1) the slopes during the elimination phase are similar.

The difference in the duration of action (Dur25) of pipecuronium 0.07 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} failed to reach statistical significance. The impression from inspection of the results, however (fig. 2), is that the duration of action would be matched more closely if we had used a larger dose of pipecuronium. Earlier studies [21, 22] have shown that pipecuronium and pancuronium have similar duration of action when the dose ratio of pipecuronium to pancuronium is approximately 80%. Our results are compatible with these findings. One patient in each group had prolonged neuromuscular blockade. Neither the clinical profile nor the treatment of each patient could account for this. The patient with prolonged blockade following pipecuronium had a low Cl (1.5 ml kg^{-1} min^{-1}), a large V^{ss} (505 ml kg^{-1}) and a long $T_{\frac{1}{2}}^{\beta}$ (332 min). Unfortunately, the patient with prolonged blockade following pancuronium was also the patient for whom we were unable to calculate the elimination phase. Overall, however, there was not a good correlation between the duration of neuromuscular blockade and any pharmacokinetic parameter.

From these comparisons we conclude that the clinical time course of action of pipecuronium and pancuronium in normal, healthy patients is similar, despite significant differences in V^{ss} and Cl.

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SEDATION FOR ENDOSCOPY: MIDAZOLAM OR DIAZEPAM AND PETHIDINE?

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SUMMARY

One hundred patients received either diazepam given with pethidine, antagonized with naloxone, or midazolam alone in a double-blind randomized study of sedation for upper gastrointestinal endoscopy. Midazolam produced better amnesia for the procedure ($P < 0.0001$) but diazepam and pethidine resulted in less retching during the procedure ($P < 0.01$) and less sedation after the procedure, as judged by a simple performance test ($P < 0.02$) and patient recall of results ($P < 0.02$).

In a previous study, i.v. diazepam (Diazemuls) given until the patient became dysarthric was compared with a fixed-dose combination of diazepam, pethidine and naloxone as sedation for endoscopy [1]. Both forms of sedation were accepted equally well by the patients and there was no difference in sedation after endoscopy, but the use of pethidine produced a significant improvement in patient co-operation during endoscopy.

Midazolam is used widely for sedation for endoscopy. Midazolam and diazepam have been compared in other studies, which have noted that midazolam produces excellent amnesia for the endoscopy and lack of venous complications [2, 3].

In this study, our aim was to compare midazolam with our preferred sedation for endoscopy, namely diazepam given with pethidine. In particular, we wished to discover if the shorter elimination half-life of midazolam would be reflected in the ability of the patient to undertake the simple performance test to assess recovery from the sedation.

PATIENTS AND METHODS

One hundred patients (50 female) undergoing elective upper gastrointestinal endoscopy were entered into a double-blind trial. Informed written consent was obtained before the patient was allocated to one of the two forms of sedation, male and female patients being randomly allocated separately. The sedation was given by an assistant and the endoscopists were unaware of the sedation received by the patients. Fifty percent of the patients received i.v. midazolam, injected slowly until the onset of dysarthria. The mean (SD) dose for males was 11.3 (4.9) mg (range 6–30 mg) and for females was 10.7 (4.3) mg (range 5–25 mg). The remainder of the patients were given a combination of i.v. diazepam (Diazemuls) 10 mg plus i.v. pethidine (50 mg if body weight less than 70 kg; 75 mg if body weight greater than 70 kg) immediately before endoscopy. Once the endoscopy was completed, the second group was given naloxone 0.4 mg i.v. to antagonize the pethidine.

Immediately after the procedure, the endoscopist completed a questionnaire on the ease of examination, patient co-operation and assessment

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of the degree of sedation. The effect of sedation was assessed using the p performance test [4] before endoscopy and 2 h after endoscopy [1]. On the morning after endoscopy, the patients were asked to complete a questionnaire concerning sedation, amnesia and their willingness to undergo a further endoscopy.

The results were analysed using the Chi-squared test with Yates' correction to assess differences between the two study groups. A simple 2×2 contingency table was used to determine the relationship between subjective and objective assessments of recovery from sedation. Matched pair analysis using Student's t test was applied to the data from the p performance test.

RESULTS

Patient details are given in table I. The groups did not differ significantly with respect to age, racial group, alcohol and smoking habits.

A complete examination of the upper gastrointestinal tract as far as the second part of the duodenum was obtained in all but one patient, who received midazolam and was impossible to examine because of inadequate sedation. The degree of sedation was judged to be similar in both groups and was considered good in 28 patients in the midazolam group and 25 patients in the combination group. There was significantly more retching in the midazolam group ($P < 0.01$) (table II). One patient in the midazolam group became markedly agitated during the endoscopy, but otherwise patient co-operation was satisfactory in both groups.

The results of the patients' questionnaire showed better amnesia for the procedure in the midazolam group ($P < 0.0001$) (table II). More patients given the combination of diazepam and pethidine could remember what the doctor had said to them 2–4 h after the endoscopy ($P < 0.02$) (table II).

Table III shows the results of the p performance test. Patients who received diazepam and pethidine antagonized with naloxone showed no

TABLE I. *Patient details. No significant differences between sedation groups*

	Midazolam group	Combination group
n	50	50
Male:Female	25:25	25:25
Age (yr)		
Average	51.0	46.3
Range	21–75	25–75
Caucasian	47	50
West Indian	2	0
Indian	1	0
No alcohol	24	21
Alcohol < 2 units/week	23	27
Alcohol > 2 units/week	3	2
Smoker	22	25
Tranquillizers	7	6

TABLE II. *Results.* P *values for significance of difference between groups*

	Midazolam group	Combination group	*P*
Endoscopist description of patient			
Co-operative	35	42	ns
Restive	9	7	
Unco-operative	6	1	
No retching	23	38	< 0.01
Some retching	19	9	
Constant retching	8	3	
Patient reports			
Memory of test			
Nothing	45	23	< 0.0001
Vaguely aware	3	20	
Fully aware	1	7	
Remember what doctor told them after test			
Yes	31	43	< 0.02
Partially	13	7	
No	5	0	

TABLE III. *Results of the* p *performance test*

	Midazolam group	Combination group	Difference between groups
Mean number of lines completed			
Before endoscopy	21.24	22.16	ns
After endoscopy	18.22	21.26	ns
Mean change	+3.02	+0.86	$P < 0.02$
Significance of mean change	$P < 0.001$	ns	

impairment in their ability to perform the test 2 h after the sedation was administered. However, patients who received midazolam showed a significant reduction in the number of lines completed after sedation (pre- minus post-endoscopy: mean change +3.02 ($P < 0.001$)). In a direct comparison between the two groups, midazolam produced significant impairment in the post-endoscopy performance test when compared with the combination sedation ($P < 0.02$). Twelve of the midazolam group and 24 of the diazepam with pethidine group had post-endoscopy scores as high as or higher than the pre-endoscopy scores, and so could be judged as recovered fully (Definition 1 [4]). There was no relationship between the subjective and objective scores of recovery (patient's recall of information and performance test ability) ($P > 0.5$).

There were no cardiorespiratory problems in either group. One patient who received diazepam, pethidine and naloxone developed a mild thrombophlebitis. Two patients, one in each group, complained of headache: one during the injection of midazolam and one after the endoscopy.

DISCUSSION

Sedation with diazepam and pethidine was better for the endoscopist than sedation with midazolam because there was less retching. This finding confirms our previous study [1]. Amnesia for endoscopy may be desirable and midazolam gave significantly better results than the combination sedation, confirming the excellent amnesic properties of midazolam reported in previous studies [2, 3, 5, 6]. However, it is also important that the patient remember information passed on while in hospital. A significantly larger number of the midazolam group were unable to remember what the doctor told them about the investigation, and their recovery, judged by the performance test, was impaired also. In addition, the patients who received midazolam were sedated more heavily on arrival at the observation ward after the endoscopy, a finding noted previously by Al-Khudhairi, Whitwam and McCloy [2]. These findings could result from the different method of administration of each benzodiazepine. The dose of midazolam was titrated against patient response, resulting in a comparatively high equivalent dose of benzodiazepine compared with the fixed dose of diazepam.

This study confirms our previous result of improved patient co-operation when an opioid analgesic drug was added to the sedation regimen. Similarly, midazolam in combination with pentazocine also produced better patient co-operation than midazolam alone [7].

From our two studies, it appears that midazolam has little advantage over diazepam alone, the excellence of amnesia for the procedure being negated by the patient's inability to retain information on the result of the investigation. Patients were still significantly sedated 2 h after endoscopy. It is essential that the patient does not drive after this procedure, as is recommended for sedation with diazepam. Midazolam in lower doses, combined with pethidine may prove as good as or better than diazepam and pethidine and a trial is indicated.

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PREMEDICATION WITH PIROXICAM IN PATIENTS HAVING DENTAL SURGERY UNDER GENERAL ANAESTHESIA WITH HALOTHANE OR ISOFLURANE

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SUMMARY

Pain, analgesic requirements, mouth opening and emesis were assessed in 60 patients who received either piroxicam 40 mg or placebo before dental surgery under general anaesthesia which included breathing either halothane or isoflurane. Patients went home on the day after surgery and completed a questionnaire concerning pain and emesis. There were four groups of 15 subjects: piroxicam–halothane, piroxicam–isoflurane, placebo–halothane or placebo–isoflurane. Pain increased at 2 and 4 h and had reduced by 18 h after surgery; there were no significant differences between the groups in pain scores. After operation, fewer patients in the piroxicam–isoflurane group required papaveretum compared with the piroxicam–halothane and placebo–halothane groups. Mouth opening was reduced between 2 and 4 h after surgery, but was less restricted after piroxicam–isoflurane than placebo–halothane. There was no difference between the groups in the incidence of emesis within 18 h of surgery. The postal questionnaire suggested that pain and emesis were reduced significantly during the 3 days after surgery in patients who had received piroxicam before surgery, compared with those who had received placebo.

Pain after dental surgery frequently requires analgesia [1], and patients who have undergone removal of impacted lower third molars usually experience the most severe pain during the first 12 h after operation [1, 2]. Oral opioids, including morphine [3], codeine [4] and dextropropoxyphene [5], are ineffective in relieving pain in this situation. Pain and swelling after dental surgery may be mediated by a local tissue response involving prostaglandins and leukotrienes, and thus may be treated more appropriately by non-steroidal anti-inflammatory drugs [6]. After oral surgery, aspirin provides better analgesia than paracetamol, presumably because of superior anti-inflammatory properties [1]. However, oral aspirin has a short duration of action, and repeated doses may be difficult to administer after surgery when nausea and vomiting occur commonly.

It may be useful to administer an oral non-steroidal anti-inflammatory drug before operation to provide analgesia immediately after surgery and perhaps reduce the requirement for parenteral postoperative analgesics. Ibuprofen and flurbiprofen both relieve pain after oral surgery [7–9], but their duration of action is rather short. Piroxicam is an enolic acid belonging to the oxicam group of non-steroidal anti-inflammatory drugs. It is absorbed rapidly after oral administration, produces analgesia within 2 h and has a prolonged effect, with a half-life of 38–45 h [10]. Single or multiple doses of piroxicam may be useful after oral surgery under local anaesthesia [11, 12]. The present study was designed to evaluate the use of a single dose of dispersible piroxicam 40 mg given before oral surgery under general anaesthesia. The effect of choice of volatile inhalation anaesthetic agent was assessed also by random allocation of patients to receive either halothane or isoflurane during the procedure.

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PATIENTS AND METHODS

Local Ethics Committee approval was granted for this double-blind study which involved 60 healthy patients undergoing third molar extraction under general anaesthesia (some subjects also had simple extraction of premolar teeth). Patients with no history of intolerance to non-steroidal anti-inflammatory drugs were premedicated with lorazepam 2–3 mg with either dispersible piroxicam 40 mg or placebo by mouth in a random manner, 2 h before surgery, which was always performed in the afternoon. I.v. papaveretum 5–7.5 mg was administered just before induction of anaesthesia with thiopentone 3–5 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was used to facilitate nasal intubation of the trachea and patients breathed either halothane or isoflurane and nitrous oxide in oxygen. The investigators were aware of the choice of volatile agent, which was random. Postoperative analgesia was available on request as i.m. papaveretum (< 59 kg 10 mg; 60–80 kg 15 mg; > 81 kg 20 mg), and emesis was treated with i.m. prochlorperazine 12.5 mg if necessary. All patients were nursed on the same ward, where staff checked patients' analgesic requirements regularly.

The same experienced surgeon performed all the operations using a standard technique. The number of third molars extracted and duration of surgery were recorded, and the surgeon was asked to rate the difficulty of the procedure (easy, mildly difficult, moderately difficult and very difficult). Patients were visited by the anaesthetist at 2, 4 and 18 h after surgery. Pain was assessed using a 10-cm visual analogue score and a four-point verbal rating scale (none, mild, moderate and severe). The time to request the first dose of postoperative papaveretum and the number of doses received were recorded. Maximum mouth opening was measured using calibrated calipers placed between the upper and lower incisors. The incidence of nausea and vomiting was noted. Patients were sent home on the morning after surgery and were asked to complete a postal questionnaire concerning pain and emesis during the 3 days after discharge from hospital.

Parametric data were analysed using analysis of variance. Visual analogue pain scores were arc-sine root transformed before two-way analysis of variance [13]. Non-parametric data were analysed using Kruskall–Wallis analysis of variance, Mann–Whitney *U*, Fisher's exact and Chi-square tests.

RESULTS

Demography (table I), type, duration and difficulty of surgery (table II) were not significantly different in the four groups of 15 patients.

There were no significant differences between the groups in pain scores during the first 18 h after surgery. In addition, males and females did not have significantly different pain scores at any time. Pain increased at the 2- and 4-h assessment ($P < 0.01$) and had reduced by 18 h ($P < 0.01$) in all four groups. Postoperative pain was not related to the duration or difficulty of surgery. Fewer patients received postoperative papaveretum after piroxicam–isoflurane compared with piroxicam–halothane ($P < 0.005$) or placebo–halothane ($P < 0.025$) (table III). The time to receive the first dose and the number of doses of postoperative opioid did not differ significantly between the groups (table III), and were not related to the duration or difficulty of surgery. Eighteen percent of all patients received two doses of opioid within

TABLE I. *Mean (SD) age, weight and sex distribution* (n = *15 in each group)*

	Age (yr)	Weight (kg)	Sex (M:F)
Piroxicam–halothane	21.5 (2.9)	61.3 (8.0)	5:10
Piroxicam–isoflurane	23.3 (3.2)	66.4 (9.5)	8:7
Placebo–halothane	23.6 (3.3)	58.0 (8.7)	4:11
Placebo–isoflurane	22.6 (4.4)	61.4 (7.4)	5:10

TABLE II. *Mean (SD) number of third molars extracted, duration of surgery and difficulty of surgery* (n = *15 in each group)*

	No. 3rd molars extracted	Duration (min)	Moderate/very difficult
Piroxicam–halothane	3.2 (1.1)	28.7 (13.3)	7
Piroxicam–isoflurane	3.1 (0.9)	24.4 (11.8)	8
Placebo–halothane	3.5 (0.7)	28.9 (14.2)	6
Placebo–isoflurane	3.3 (1.1)	24.9 (15.2)	9

TABLE III. *Percent of patients requiring postoperative analgesia, mean (SD) time to receive first dose of analgesia and number of patients requiring two doses of analgesia within 18 h of surgery. *Significantly fewer patients required analgesia after piroxicam–isoflurane than after piroxicam–halothane or placebo–halothane* ($P < 0.05$: *Fisher's exact test*)

	Requiring analgesia (%)	Time to analgesia (h)	Two doses analgesia
Piroxicam–halothane	87	2.7 (1.9) ($n = 13$)	3
Piroxicam–isoflurane	27*	5.8 (2.7) ($n = 4$)	0
Placebo–halothane	73	3.5 (2.6) ($n = 11$)	4
Placebo–isoflurane	60	3.7 (2.8) ($n = 9$)	4

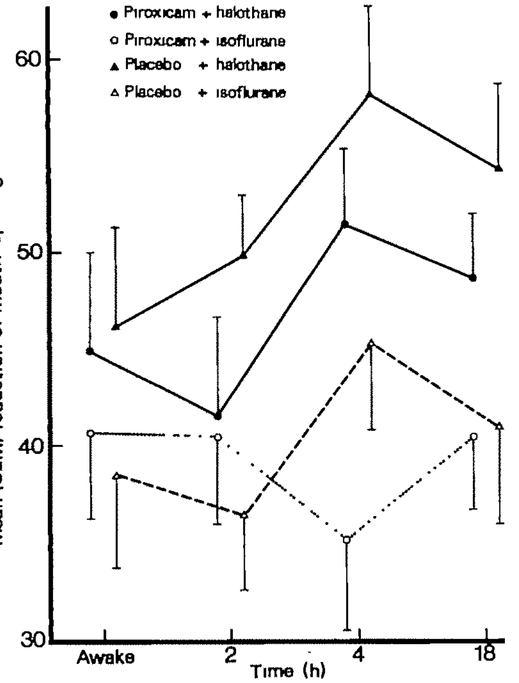

FIG. 1. Mean (SEM) restriction in mouth opening in each group at each postoperative assessment. Mouth opening reduced significantly between 2 and 4 h after surgery ($F = 2.90$, $P < 0.05$), mouth opening more restricted after placebo–halothane than after piroxicam–isoflurane ($F = 3.02$ $P < 0.05$) (two-way analysis of variance with repeated measures on one factor).

18 h of surgery, but none of these was in the isoflurane–piroxicam group.

Mouth opening was reduced significantly between 2 and 4 h after surgery ($P < 0.05$), and was more restricted in the placebo–halothane group compared with the piroxicam–isoflurane group ($P < 0.05$) (fig. 1). There was no significant correlation between mouth opening and difficulty of surgery, postoperative pain or analgesic requirements.

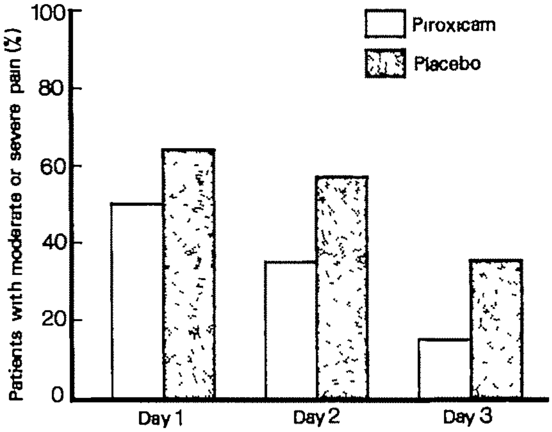

FIG. 2. Percent of subjects with moderate or severe pain on a four-point scale during the 3 days after surgery. Overall pain was significantly worse after placebo than after piroxicam ($Z = 2.06$, $P < 0.05$) (Mann–Whitney U test).

There was no significant difference between the groups in the overall incidence of emesis during the first 18 h after surgery, with 20 % nausea and 17 % vomiting.

Ninety-two percent of patients returned the questionnaire documenting pain and emesis during the first 3 days after surgery. These were analysed comparing the placebo and piroxicam groups and disregarding the effect of the volatile anaesthetics. During the first 3 days after discharge from hospital the placebo group complained of significantly more pain than the piroxicam group ($P < 0.05$); on the 3rd day after surgery, 36 % of the placebo group experienced moderate to severe pain compared with 16 % of the piroxicam group (fig. 2). More patients reported severe pain after placebo (29 %) than after piroxicam (8 %) ($P < 0.05$). After discharge from hospital, the incidence of emesis was significantly greater in the placebo group (39 %) than the piroxicam group (15 %) ($P < 0.05$).

DISCUSSION

The pattern of pain in this study was similar to that noted in previous studies [1, 2]. Pain scores during the first 18 h after surgery were not influenced by the use of piroxicam or the choice of volatile anaesthetic agent. However, the pain scores may have been modified by the administration of postoperative parenteral analgesia. Patients who had received piroxicam–isoflurane required less postoperative papaveretum, and therefore presumably had less pain, than those who had been given piroxicam–halothane or placebo–halothane.

Some inhalation anaesthetics, for example trichlorethylene, methoxyflurane, enflurane [14] and isoflurane [15] are analgesic when inhaled in low concentrations. Isoflurane may therefore have contributed to analgesia in the early postoperative period. It has been suggested that halothane has poor analgesic properties and may even cause increased sensitivity to pain in volunteers [16]. Although this finding has since been questioned [17], the halothane groups did seem to fare worse than the isoflurane groups immediately after surgery.

Mouth opening was restricted in all four groups, especially between 2 and 4 h after surgery. Duration and difficulty of surgery were not predictive of pain or restriction of mouth opening. Therefore prescription of postoperative analgesia should not be based on these criteria. Reduced mouth opening did not correlate with pain, suggesting that restriction of mouth opening may result from swelling and oedema. The piroxicam–isoflurane patients had better mouth opening than the placebo–halothane patients, suggesting that there may be an interaction between piroxicam and isoflurane. A synergistic effect is postulated, as the isoflurane–piroxicam patients were consistently better than the other groups during the first 18 h after surgery.

Opioids were given after surgery in the present study, as is the standard practice in our unit. However, the use of opioids after oral surgery is of questionable value and may lead to increased emetic sequelae. In the present study, nausea and vomiting were seen in 33 % of the patients within 18 h of surgery, but emesis was not increased by the use of piroxicam. If postoperative emesis is a problem when analgesia is required, parenteral non-steriodal anti-inflammatory drugs may be of value.

The results of the postal questionnaire showed that pain and emesis after discharge from hospital following dental surgery may be more common than is appreciated. Approximately 33 % of patients who had placebo experienced moderate to severe pain and nausea or vomiting during the 3 days after surgery. Patients who had received piroxicam had significantly less pain and emesis during this time. The pharmacokinetics of piroxicam would explain the prolonged analgesia, but the lower incidence of nausea and vomiting were surprising. The results of the questionnaire should be interpreted with caution, as it did not include questions concerning the use of analgesics after discharge from hospital, and the placebo group may have required more supplementary analgesia, which resulted in emesis.

It may be an advantage to give piroxicam for a longer period before surgery as it is necessary to administer it for at least 3 days to achieve maximum anti-inflammatory effect [18]. Pain relief is poor if patients are allowed to self-prescribe analgesics after oral surgery [1], therefore it may be valuable to prescribe piroxicam for a few days after surgery, when the dispersible form is particularly useful, as it is easy to swallow.

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COMPARISON OF PROPOFOL AND THIAMYLAL FOR INDUCTION AND MAINTENANCE OF ANAESTHESIA FOR OUTPATIENT SURGERY

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SUMMARY

In an open, randomized study we have compared the safety and efficacy of propofol with thiamylal for induction and maintenance of anaesthesia supplemented by nitrous oxide in elective termination of pregnancy. Induction of anaesthesia was achieved with either propofol 2.5 mg kg^{-1} or thiamylal 4.0 mg kg^{-1} followed by maintenance with 70% nitrous oxide in oxygen and repeat boluses of 25% of the induction dose i.v. as indicated clinically. Both drugs induced and maintained anaesthesia reliably, with some minor differences. Recovery from propofol was significantly more rapid. The patients in the propofol group were alert and orientated early in the postoperative period, with less nausea or vomiting. Propofol has properties that are of particular benefit in anaesthesia for ambulatory surgery.

Propofol was first used clinically in 1977 [1]. The original Cremophor formulation was changed to an aqueous emulsion [2–4], which is thought to be less likely to produce anaphylactoid reactions [5]. It is metabolized rapidly by the liver, and possibly by the lungs, with excretion of the metabolites in urine [6]. After an i.v. injection, propofol has a short distribution phase and a rapid metabolic clearance from blood which approximates to liver blood flow. The terminal elimination half-life is between 300 and 500 min. Thus propofol is potentially useful for induction and maintenance of anaesthesia in ambulatory surgical patients.

Thiamylal is a commonly used ultra short-acting barbiturate with a potency 1.1 times that of thiopentone and clinical properties virtually identical to those of thiopentone. The present study was designed to evaluate the safety and efficacy of propofol compared with thiamylal when used for the induction and maintenance of anaesthesia in elective terminations of pregnancy. Observations during anaesthesia were carried out in an open, "unblinded" manner, while recovery observations were "blinded".

PATIENTS AND METHODS

Forty female patients, ASA class I or II, aged between 18 and 37 yr, were studied during elective termination of pregnancy on an outpatient basis. Patients gave written informed consent to the study, which had been approved by the Institutional Review Board. Patients were excluded with hepatic, renal, haematological, cardiac, respiratory or metabolic disease, gross obesity, or if they gave a history of allergy or any previous adverse response to general anaesthesia.

On arrival of the patient in the operating room a three-lead electrocardiograph was attached and arterial pressure measured using an automated machine. An 18-gauge catheter was inserted into a convenient vein on the forearm or hand and an infusion of lactated Ringers solution in 5% dextrose started. All patients were premedicated with glycopyrrolate 0.2 mg i.v. 5 min before induction of anaesthesia. The patients were assigned randomly to receive either propofol or thiamylal.

Propofol 2.5 mg kg^{-1} or thiamylal 4.0 mg kg^{-1} was administered over 20–30 s to induce anaesthesia. The patient was observed for the next 3 min while spontaneously breathing 100% oxygen.

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Observations of heart rate and arterial pressure were made at 1-min intervals. If the patient failed to lose consciousness (as defined by loss of eyelash reflex and lack of response to verbal command), the induction was considered unsatisfactory. When necessary, repeat boluses of 25% of the induction dose were administered to complete induction.

Anaesthesia at the commencement of surgery was maintained with 70% nitrous oxide in oxygen. Repeat injections of 25% of the induction dose for maintenance of anaesthesia were administered as indicated clinically by the level of anaesthesia. Indication for repeat boluses included increased ventilation, vocalization, swallowing or movement in response to surgical stimuli. Arterial pressure, heart rate, electrocardiogram and rate of ventilation were monitored throughout. The duration of apnoea was recorded if it occurred. During the procedure, oxytocin 10 units was injected i.v. after evacuation of the uterus.

Recovery time was assessed by a second observer who was unfamiliar with the type of anaesthesia given. This observer measured the elapsed time from the termination of anaesthesia (discontinuation of nitrous oxide) to the time of spontaneous eye-opening, to response to verbal command, and to full orientation (as defined by the patient being able to give her correct birthdate). In the recovery room, observation was continued and arterial pressure and heart rate changes at 5-min intervals were recorded. The occurrence of nausea, vomiting, drowsiness, headache, shivering or any venous complication was noted.

Unless otherwise indicated, data are presented as mean and standard deviation (SD), and the two groups were compared by the unpaired Students' *t* test and the Fisher exact test, with a significance level of $P < 0.05$.

RESULTS

Forty female patients were studied in random order, 19 receiving propofol and 21 thiamylal. There was no significant difference between the two groups with regard to mean age, weight or duration of pregnancy (table I).

Anaesthesia induction times from the beginning of the bolus injection, were not different clinically or statistically between the two groups (table II). Propofol 2.5 mg kg^{-1} induced anaesthesia more reliably than did thiamylal 4.0 mg kg^{-1} ($P < 0.05$). All patients receiving propofol were anaesthetized after a single induction dose, while in the thiamylal group, two patients required an additional bolus before losing consciousness, and two additional patients receiving thiamylal awoke during the 3-min observation period while breathing 100% oxygen. Side effects during induction and the 3-min observation period totalled 16 in the propofol group and 10 in the thiamylal group, but there was no statistically significant difference between the groups (table III). Small and weak spontaneous movement of the limbs occurred in four patients in the propofol group and in one patient in the thiamylal group. These movements were easy to control and did not interfere with surgery. Pain on injection occurred in four patients in the propofol group who all had an i.v. cannula on the back of the hand.

During the 3-min observation period (breathing

TABLE I. *Patient characteristics (mean (SD)). No significant difference between groups*

	Propofol	Thiamylal
Total	19	21
Age (yr)	26 (6.2)	27 (6.5)
Weight (kg)	61 (10.6)	57 (7.8)
Duration of pregnancy (weeks)	10.3 (4.1)	10 (3.5)

TABLE II. *Mean (SD) times for induction of anaesthesia. No significant difference between groups*

	Propofol ($n = 19$)	Thiamylal ($n = 21$)
Loss of response to verbal stimuli (s)	51.8 (7.5)	54.0 (10.5)
Loss of eyelash reflex (s)	61.5 (10.8)	69.8 (16.7)

TABLE III. *Incidence of side effects with propofol and thiamylal during induction of anaesthesia. No significant difference between groups*

	Propofol ($n = 19$)	Thiamylal ($n = 21$)
Coughing	2	3
Laryngospasm	0	1
Spontaneous movement	4	1
Pain at injection site	4	1
Apnoea > 30 s but < 60 s	6	4
Apnoea > 60 s	0	0

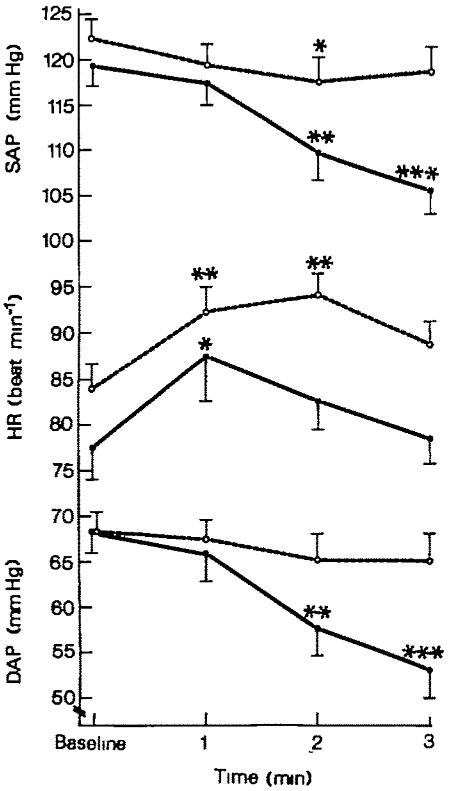

FIG. 1. Changes in systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and heart rate (HR) (mean, SEM bars) after propofol (——) or thiamylal (——). Within group differences (measured from baseline): * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

TABLE IV. *Anaesthesia maintenance—mean times (SD). No significant difference between groups*

	Propofol (n = 19)	Thiamylal (n = 21)
Time between supplementary doses (s)	207.1 (61.6)	192.4 (60.7)
Duration of anaesthesia (min)	13.7 (1.4)	14.4 (1.0)

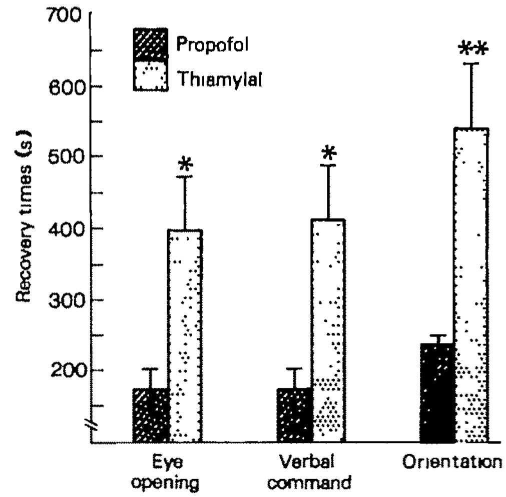

FIG. 2. Recovery times (mean, SEM bars) from discontinuation of anaesthesia (nitrous oxide turned off) till eye opening, response to verbal command and orientation. * $P < 0.05$; ** $P < 0.01$.

TABLE V. *Incidence of postoperative side effects*

	Propofol (n = 19)	Thiamylal (n = 21)	P
Nausea or vomiting	0	5	< 0.01
Thrombosis at injection site	0	0	ns
Drowsiness	0	0	ns
Hiccup	0	1	ns
Headache	0	0	ns

100 % oxygen with no surgical stimulation) haemodynamic variables were different between the propofol and the thiamylal groups (fig. 1). A small decrease in systolic arterial pressure was noted in both groups, but was more significant in the propofol group where it reached 11 % below baseline at 3 min. Diastolic pressure was significantly lower with propofol, being 15 % below baseline at 2 min and 22 % below baseline at 3 min. Heart rate increased significantly in both groups at 1 min and remained higher with thiamylal. During maintenance of anaesthesia, heart rate and arterial pressure were stable with both agents, without a significant difference between the groups. No arrhythmias or other electrocardiographic changes occurred during induction or maintenance of anaesthesia with either agent.

There were no reports of awareness or untoward effects during maintenance of anaesthesia in each group. The mean times between supplementary doses of drug and the mean duration of anaesthesia were not different significantly between the two groups (table IV). Recovery from discontinuation of nitrous oxide was significantly more rapid in the propofol group than in the thiamylal group (fig. 2).

Side effects within the first 2 h after surgery were few in both groups, but there was a significantly higher incidence of nausea and vomiting in the thiamylal group (table V).

DISCUSSION

Propofol is a suitable agent for the induction and maintenance of general anaesthesia for ambulatory surgical patients. Propofol 2.5 mg kg^{-1} induced general anaesthesia more reliably than did thiamylal 4.0 mg kg^{-1}. Induction with propofol was rapid and smooth with a low incidence of coughing or laryngospasm. However, in the propofol group mild pain on injection and spontaneous small movements of the limbs were more common. Apnoea during induction occurred more frequently with propofol, but was of short duration (less than 30 s) and presented no difficulty clinically. Apnoea did not occur with either agent during anaesthesia maintenance. Both systolic and diastolic pressures decreased more with propofol than with thiamylal during the 3-min observation period. The hypotension with propofol was accompanied by a small increase in heart rate, less so than the increase in rate with thiamylal.

These findings with propofol represent probably a dose-related cardiovascular depression, although they were not clinically significant in this group of healthy patients. This effect, which has been demonstrated with both the original formulation and the aqueous emulsion, results primarily from a decrease in systemic vascular resistance and possibly in cardiac output [7–9]. Several authors have reported hypotension in the majority of patients receiving doses of propofol greater than 2.0 mg kg^{-1} [2, 10]. It is possible that the 2.5-mg kg^{-1} induction dose, used in our study, represented a relative overdose as all patients were anaesthetized successfully with this single dose of propofol, and only two of the 19 required a 25% supplement for slight limb movements towards the end of the 3-min observation period. However, many authors have used a propofol induction dose of 2.5 mg kg^{-1} when comparing this drug with other induction agents [11–14].

Recovery was rapid following propofol anaesthesia. Time to eye-opening, response to verbal command and orientation (as determined by correct birthdate) were all significantly faster than with thiamylal. However, the clinical significance of this is debatable as, within 20 min, the patients in both groups were clear-headed with very little drowsiness and there was no difference between the groups in time to discharge. Absence of nausea or vomiting following propofol was also noteworthy, especially considering the nature of the surgical procedure. No thrombosis occurred at the injection site with either agent, although a second 24-h follow-up may have revealed some instances.

In conclusion, both propofol and thiamylal provide a smooth, rapid induction of anaesthesia with minor side effects. Maintenance is easy to control using nitrous oxide and intermittent doses of either agent. Recovery from propofol is more rapid, with significantly less postoperative nausea or vomiting than with thiamylal. Propofol appears to be a suitable i.v. anaesthetic agent for ambulatory patients.

ACKNOWLEDGEMENT

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GASTROINTESTINAL MOTILITY AND GASTRIC pH AND EMPTYING FOLLOWING INGESTION OF DIAZEPAM

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SUMMARY

The effects of diazepam on antroduodenal motility, gastric pH and gastric emptying rate were investigated in 10 volunteers. Gastric emptying was assessed using paracetamol absorption and antroduodenal motility and pH by means of a perfused multilumen tube. On the first study day, the volunteers received paracetamol in phase I after the occurrence of one complete interdigestive motility complex (IDMC). Diazepam was given on the second study day at the beginning of the first phase I and paracetamol was given one IDMC later. The rate of absorption correlated with motility ($P < 0.03$). Some volunteers were fast absorbers on the first study day and slow on the second, indicating that absorption rate is not constant, but dependent on gastroduodenal motility. Diazepam tended to increase the gastric emptying rate and enhanced the amplitude of contractions and the motility index during phase II ($P < 0.02$). Gastric pH increased after ingestion of diazepam ($P < 0.05$).

Premedication with benzodiazepines by mouth is used widely and is not usually associated with an increased risk of pulmonary aspiration [1]. Previous studies have shown a decrease in the volume and acidity of the stomach contents after ingestion of diazepam [2,3]. Several factors influence the absorption of drugs administered by mouth, including gastrointestinal activity [4–6].

This study was undertaken to investigate the effects of diazepam on antroduodenal motility, gastric pH and gastric emptying rate.

SUBJECTS AND METHODS

Ten healthy volunteers (seven men and three women, aged 22–30 yr) without gastrointestinal symptoms participated in the study. None was a regular user of any drugs and no medication was taken in the week preceding each of the two study days, which were 8–14 days apart. All subjects fasted overnight before and during the investigations.

Informed consent was obtained from all individuals before the studies, which were approved by the local Ethics Committee.

Antroduodenal motility was recorded using a six-lumen polyvinylchloride tube with an external diameter of 4.7 mm (GIMK-14R7-250 A, William Cook Europe A/S) [7]. Each lumen had an internal diameter of 0.7 mm and a side-hole opening sited at various distances from the tip. The manometric assembly, complete with pH electrode, was passed through a nostril and placed, under fluoroscopic control, so that the tip of the tube was near to the ligament of Treitz.

Side openings at 2, 18, 26, 34 and 42 cm from the tip of the tube were arranged so that two were placed in the gastric antrum (A1 proximal, and A2 distal) and three in the duodenum (D1, D2 and D3). The lumina were perfused continuously with distilled water at a rate of $0.2\ \mathrm{ml\ min^{-1}}$ per channel, utilizing a pressure infusor. Intraluminal pressure was measured by strain gauge transducers (Gould-Statham) and recorded on a multichannel paper chart recorder (Mingograf 805, Siemens Elema).

A pH microelectrode (GK 2801-C, Radiometer,

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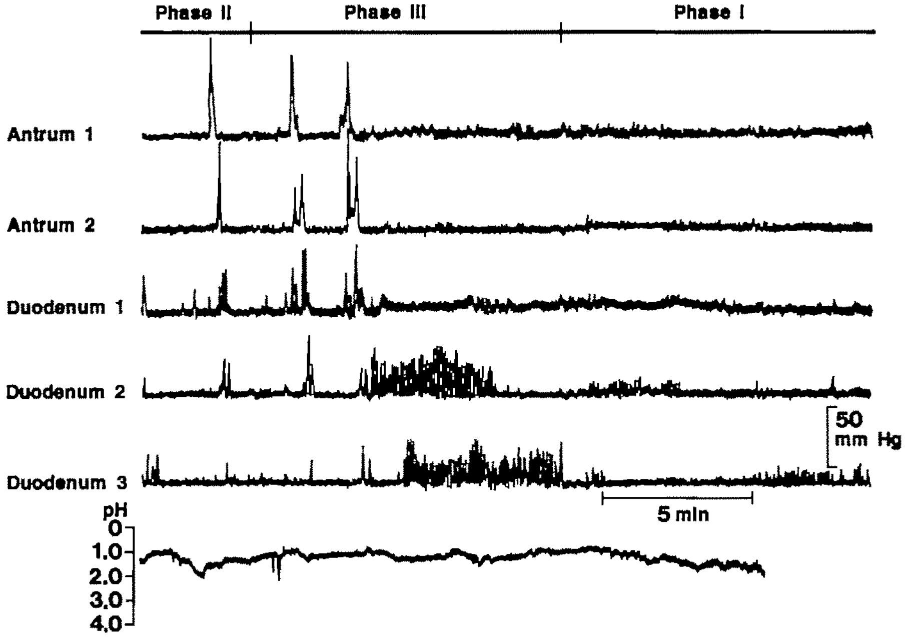

FIG. 1. Antroduodenal motility in the fasting stage following diazepam. A1 proximal and A2 distal antrum, D1 proximal, D2 middle and D3 distal duodenum.

Copenhagen) was passed through one lumen and attached to the side of the manometric catheter between the two antral recording sites. The pH electrode was calibrated with commercial buffer solutions (pH 4.01 and 1.09). Gastric antral pH was displayed continuously on a pH-meter (Radiometer, Copenhagen) and recorded on the paper chart recorder. All measurements were recorded also via an interface on a multichannel tape recorder (TEAC xR-510), for later data compression and analysis.

The rate of gastric emptying was assessed by paracetamol absorption after oral ingestion [8–10].

All the investigations commenced at 7 a.m. and the subjects remained supine throughout the investigations. Paracetamol was administered after one complete interdigestive motility complex (IDMC) immediately after the second phase III on the first study day. An IDMC was defined as the motility pattern from the beginning of one phase III to the beginning of the next (fig. 1) [11]. Each individual received paracetamol 20 mg kg^{-1} (median 20.47 mg kg^{-1}) as Panodil tablets, given as a combination of whole and half 500-mg tablets, with 40 ml of water.

Diazepam was given immediately after the first phase III on the second study day. Each individual received diazepam 0.25 mg kg^{-1} (0.23–0.27 mg kg^{-1}) as Stesolid tablets, given as whole and half 5- or 10-mg tablets with 40 ml of water. One IDMC later, paracetamol 20 mg kg^{-1} was administered after the second phase III. Blood samples were taken at 15, 30, 60, 90, 120 and 180 min after ingestion of paracetamol on both study days. Antroduodenal motility and gastric pH were measured continuously until the last blood sample had been taken.

Data analysis

The recordings of motility were assessed manually and each phase of the IDMC was identified and assessed separately [11].

The duration of the quiescent phase I was noted. Phase II, which is characterized by persistent irregular contractions, was assessed for duration, frequency and amplitude of contractions and the motility index (frequency × amplitude) calculated. Each phase II was divided into 5-min intervals for assessment of frequency and average amplitude of contraction at each recording site. Phase III of the IDMC was defined as a coordinated burst of activity propagated caudad. Each phase III was assessed for its duration at each site, frequency, velocity of propagation (cm min^{-1}) and amplitude of contraction. "Incomplete" phase III periods, defined as those with only antral or duodenal components, were also noted.

Serum paracetamol concentrations were measured by high pressure liquid chromatography [12]. Paracetamol absorption was assessed from serum concentrations at each sampling time, the peak paracetamol concentration (*C*max), the time to reach the peak (*t*max) and the area under the serum concentration curves (AUC) for each of the study days and correlated with the pattern of motility.

The motility data for each phase of the IDMC and pH with and without diazepam were pooled and compared for each of the study days.

The median of the highest and lowest antral pH was calculated for each 5-min epoch.

Statistical analysis

Statistical analysis was carried out with the Mann–Whitney, Kruskall–Wallis, Fisher's exact and Spearman rank sum tests. Values are given as medians with range or quartile spans, or both. $P < 0.05$ was considered significant.

RESULTS

Twenty-five IDMC (two to four in each subject) were observed on the first study day during the recording period, which was a median of 279 (216–464) min. Thirty IDMC (two to four in each subject) were observed on the second study day following ingestion of diazepam. Recording time was a median of 250 (220–342) min.

The cycle duration varied considerably both between and within subjects and with and without diazepam. Table I shows the duration of IDMC and the duration of the phases I, II and III after ingestion of paracetamol on the first and second study days. No significant difference was found between the study periods.

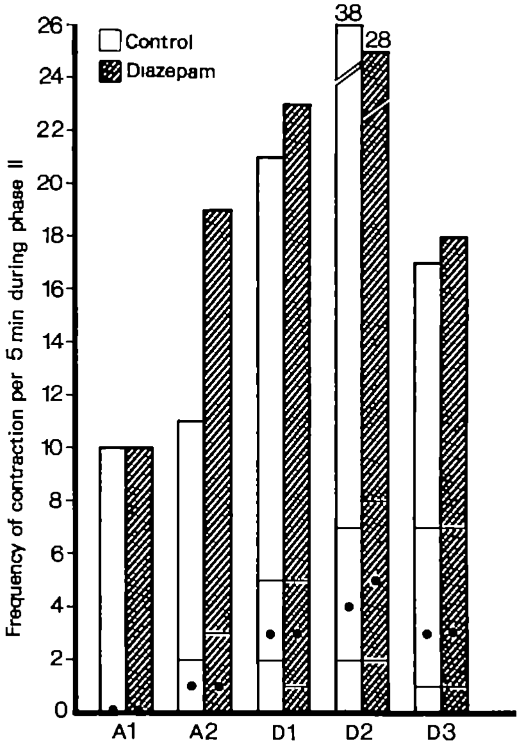

FIG. 2. Frequency of contractions during phase II on the control day (open columns) and following diazepam (cross-hatched columns). Values are medians (●) with quartile spans (–) and range.

Phase II motility and pH

Diazepam did not alter the frequency of antral or duodenal contractions (fig. 2), but increased the amplitude of contraction in the gastric antrum and the proximal duodenum (fig. 3). The motility index increased in both antrum and duodenum (fig. 4). A narrow range of pH values was observed in the control study following paracetamol, the median (range) of the lowest and highest values being 1.4 (0.9–1.7) and 2.4 (1.3–2.8), respectively. Diazepam reduced the secretion of acid by the

TABLE I. *Duration (min) of IDMC and phases I, II and III in the control period and following diazepam. Median values (range)*

	n	IDMC	Phase I	Phase II	Phase III
Control	25	90 (47–161)	20 (7–53)	49 (20–133)	6.5 (4–13)
Diazepam	30	68 (37–113)	19 (5–45)	38 (3–135)	7.5 (3–15.5)

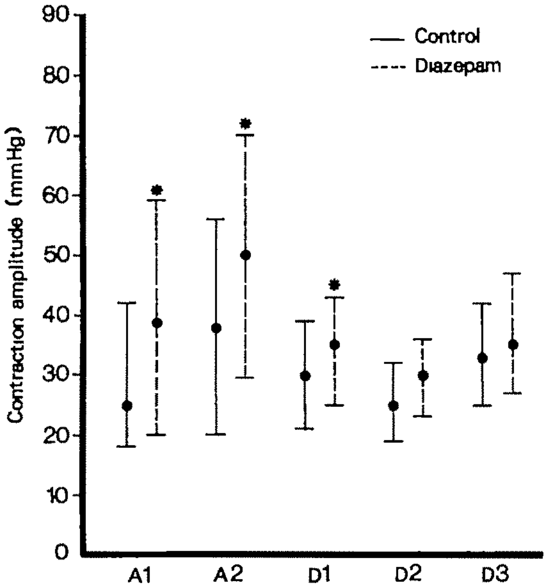

FIG. 3. Amplitude of contraction during phase II in the control period and after diazepam. Values are medians with quartile spans. $^*P < 0.05$ compared with control.

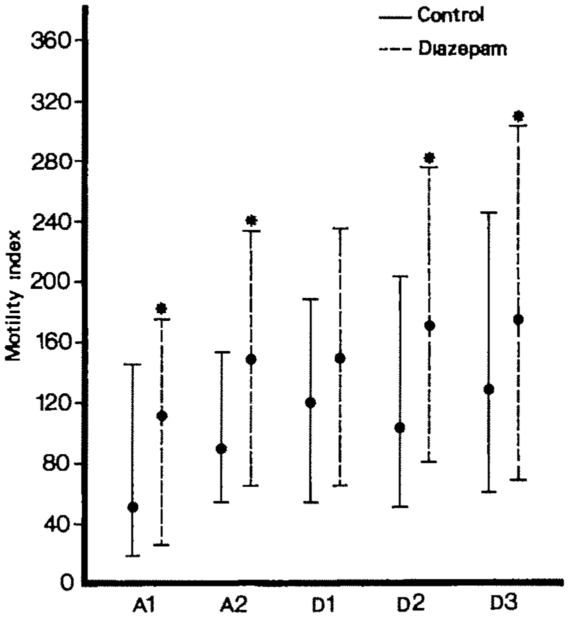

FIG. 4. Motility index during phase II in the control period and after diazepam. Values are medians with quartile spans. $^*P < 0.05$ compared with control.

stomach, the median (range) values being 2.1 (1.2–3.5) and 2.9 (1.5–4.6), respectively ($P < 0.01$).

Phase III motility and pH

Diazepam did not affect the frequency of occurrence of phase III of the IDMC. After ingestion of paracetamol, 19 phase III periods were recorded on the first study day and 23 on the second. Twenty-three per cent of the phase III periods were complete with antral activity on the control day, compared with 43.8% following diazepam. The median duration of phase III at all measuring sites was longer both with and without diazepam when an antral component was present (table II) ($P < 0.01$). The duration increased at the distal measurement sites. The frequency and amplitude of contraction did not differ between the two study days (table III).

The velocity of propagation following diazepam

TABLE II. *Duration (min) of phase III (with (+) and without (−) antral activity) in control measurements and following diazepam. Median values (range). *P < 0.01 compared with phases without antral activity*

	Control		Diazepam	
	+antral	−antral	+antral	−antral
Antral activity				
A1	2.2	—	3.2	—
	(1.0–3.2)		(1.5–4.2)	
A2	1.0	—	2.3	—
	(1.0–2.0)		(1.2–3.6)	
Duodenal phase III				
D1	1.4	1.1	3.0	0.5
	(0.6–1.5)	(0.4–1.4)	(0.6–6.4)	(0.4–3.2)
D2	5.1	3.5	7.1*	4.8
	(2.2–6.3)	(1.4–7.0)	(2.4–14.0)	(2.2–6.5)
D3	6.4*	4.2	7.4*	5.3
	(3.5–8.3)	2.6–8.5)	(5.2–9.2)	(2.2–7.2)

TABLE III. *Frequency of contractions* (min^{-1}) *and amplitudes* (*mm Hg*) *of contractions during phase III at antral* (*A1, A2*) *and duodenal* (*D1, D2, D3*) *sites. Median values* (*range*)

	Frequency		Amplitude	
	Control	Diazepam	Control	Diazepam
Antral				
A1	3.4 (3.3–3.7)	3.4 (3.2–3.6)	26.3 (18.6–36.2)	35.4 (25.9–42.7)
A2	3.5 (3.0–4.0)	3.6 (3.1–3.9)	30.0 (14.2–97.4)	51.6 (32.5–70.8)
Duodenal				
D1	9.1 (7.5–12.1)	9.9 (6.6–11.1)	39.9 (17.8–70.0)	32.6 (24.6–50.8)
D2	11.6 (9.8–12.9)	11.2 (9.7–12.1)	28.9 (11.2–51.7)	35.4 (23.9–48.8)
D3	11.6 (10.6–13.3)	11.6 (10.1–12.8)	41.9 (22.0–72.0)	44.3 (16.2–61.4)

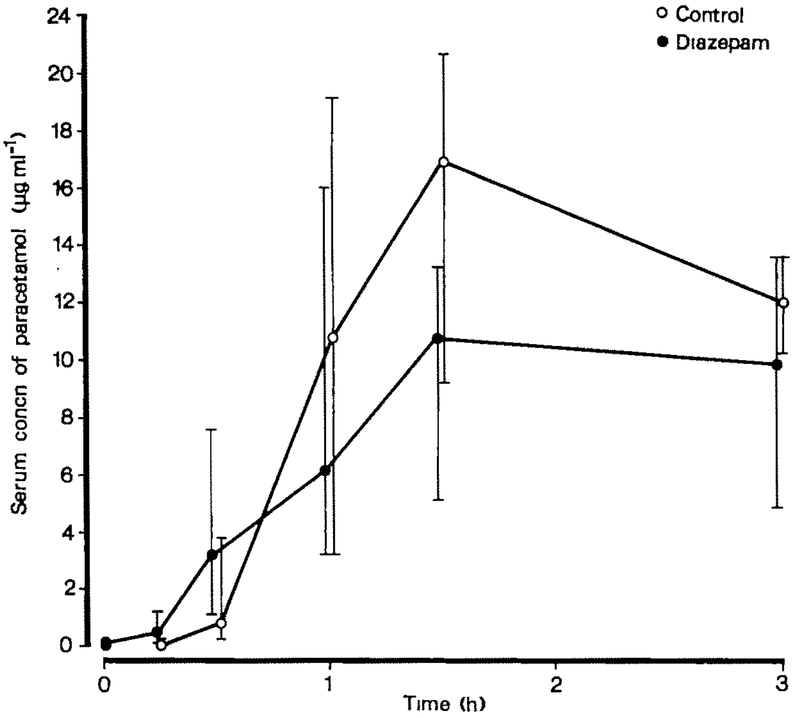

FIG. 5. Absorption curves for paracetamol with and without diazepam. ○ = Control measurements; ● = after diazepam. Values are medians with range.

was unchanged in the gastric antrum and proximal duodenum, but decreased in the distal duodenum (table IV) ($P < 0.05$).

The pH values during phase III were increased following diazepam, the median lowest and highest values (range) in the control period being 1.4 (0.5–3.6) and 1.8 (0.6–4.2), respectively, and 2.5 (0.9–6.8) and 3.4 (1.6–7.2), respectively ($P < 0.01$) following diazepam.

Gastric emptying

Paracetamol was given a median of 95 (58–175) min after diazepam. The absorption curves for the two study days are shown in figure 5. The rate of

TABLE IV. *Velocity of propagation* (*cm* min^{-1}) *of the contraction wave during phase III at antral* (*A2*) *and duodenal* (*D1, D2, D3*) *sites. Median values* (*range*). $^{*}P < 0.05$ *compared with control*

Recording site	Control	Diazepam
A1	—	—
A2	14.0 (3.2–30.0)	10.6 (5.5–39.0)
D1	9.7 (6.6–39.0)	10.6 (2.4–21.8)
D2	9.9 (7.0–21.8)	10.6 (3.9–24.0)
D3	9.1 (2.3–39.9)	6.5* (3.9–21.8)

TABLE V. *Time* (*tmax*) (*min*) *to reach peak concentration* (*Cmax*) ($\mu g\ ml^{-1}$) *of paracetamol in fast, medium and slow absorbers of paracetamol. Median values* (*range*)

	tmax	Cmax
Fast		
Control	60	20.0 (12.0–24.9)
Diazepam	30 or 60	20.3 (16.0–35.6)
Medium		
Control	90	20.3 (16.2–25.3)
Diazepam	90 or 120	14.6 (13.7–21.2)
Slow		
Control	180	10.2 (9.4–11.9)
Diazepam	180	4.9 (2.5–4.8)

TABLE VI. *Phase II characteristics* (*median* (*range*)) *for the fast, medium and slow absorbers.* + = *Present;* − = *absent. Motility index = frequency × amplitude* $^{*}P < 0.01$ *compared with fast absorbers*

	Duration (min)	Antral component	Motility index A1
Fast			
Control	44 (33–60)	+	233 (155–355)
Diazepam	34 (26–41)	+	265 (165–710)
Medium			
Control	123* (80–133)	+	95 (20–265)
Diazepam	102* (70–170)	+	305 (193–1855)
Slow			
Control	52 (20–83)	−	0
Diazepam	42 (31–70)	−	0

gastric emptying did not differ significantly between the two study days, but gastric emptying tended to increase following diazepam ($P = 0.052$ at 15 min and $P = 0.062$ at 30 min for serum concentrations of paracetamol).

No paracetamol was absorbed during phase I. Three patterns of absorption were seen on both study days. One group were fast absorbers, another medium and the third slow. Cmax and tmax for the three groups are shown in table V. Only two of the volunteers had the same pattern of absorption during the two study days. The number of fast, medium and slow absorbers did not change following diazepam.

The patterns of absorption correlated with the patterns of motility on both study days (fig. 6) ($P < 0.03$ and $P < 0.02$). The characteristics of the motility pattern during phase II are shown in table VI. The duration of phase II was longer in the group of medium absorbers than in the group of fast absorbers ($P < 0.01$).

DISCUSSION

Many drugs alter the rate of gastric emptying, either by an effect on smooth muscle or by influencing the release of gastrointestinal hormones which modulate gastrointestinal activity. There are few studies in man that demonstrate the magnitude and significance of these effects [6, 13].

Diazepam is used widely as a tranquillizer and as a premedicant before anaesthesia, and is absorbed better after oral than after i.m. administration, the same dose giving higher peak concentrations [14, 15]. Paracetamol was administered approximately 1.5 h after the diazepam, when the plasma concentration should have been close to its peak value [16]. The treatments were not given in random order, so that the presence of normal antroduodenal motility could be ensured in each volunteer before proceeding to the study proper. There is no reason to presume that this would have influenced the results.

The actions of diazepam on antroduodenal motility are probably mediated by its actions on higher regulatory structures in the central nervous system through the cholinergic vagal fibres which enhance contractions [7, 17]. The acidity of the stomach contents was reduced following diazepam, probably through a similar mechanism.

Serum paracetamol concentrations were used in this study as an index of gastric emptying rate. Paracetamol has often been used as a model for absorption studies as it is a weak acid (pK_a 9.5) and is largely un-ionized in the stomach. It is not absorbed from the stomach, but is absorbed rapidly from the small intestine and its rate of absorption is an indirect measure of gastric emptying [8].

No paracetamol was absorbed during phase I, and the administration of the drugs with water did not itself provoke any contractions. Diazepam

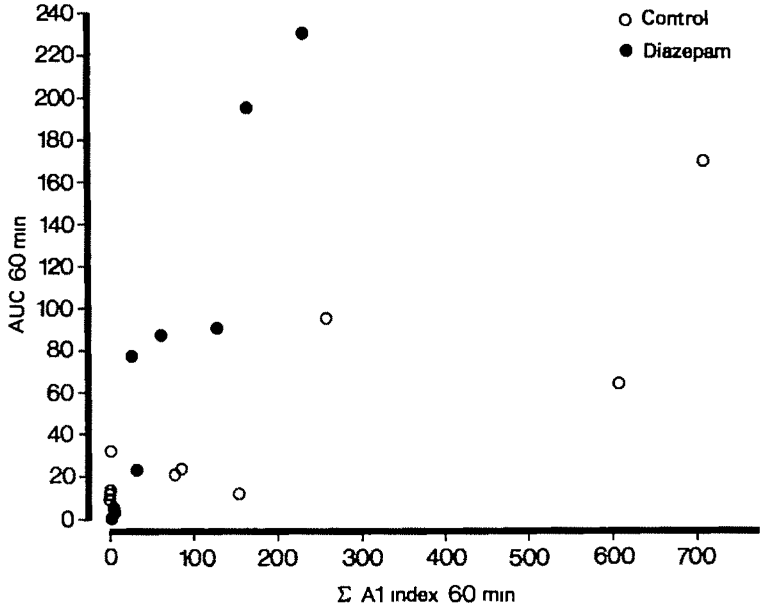

FIG. 6. Relationship between the AUC for paracetamol 60 min after ingestion and the motility index at point A1 (Σ A1 index) at the same time. ○ = Control measurements; ● = after diazepam. Correlation by Spearman test: control Rho $P = 0.023$; diazepam Rho $P = 0.003$.

tended to accelerate the rate of gastric emptying, probably by increasing the strength of contractions during phase II. The rapidity of paracetamol absorption depended partly upon the occurrence of antral activity and partly upon the duration of phase II. The occurrence of antral contractions increased towards the end of phase II and the rate of absorption increased accordingly.

It was noted that some volunteers were fast absorbers on the first study day and slow on the second. It would appear that the pattern of absorption is not constant, but varies in parallel with the pattern of antroduodenal motility.

We conclude that diazepam increases the amplitude of contractions and the motility index during phase II of the IDMC and reduces the acidity of the stomach contents.

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USE OF I.M. RANITIDINE FOR THE PROPHYLAXIS OF ASPIRATION PNEUMONITIS IN OBSTETRICS

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AND R. CATTERMOLE

SUMMARY

Twenty patients who underwent elective Caesarean section received ranitidine 150 mg by mouth 8–14 h, and 50 mg i.m. 90 min, before surgery. Intraoperative gastric aspiration resulted in contents with a pH > 2.5 and volume < 25 ml in all patients (mean pH 6.5 (SD 0.8); mean volume 9.0 (SD 7.2) ml). Sixty patients in labour, who received ranitidine 50 mg i.m. 6-hourly, underwent emergency surgery. Half of this group received, in addition, a single preinduction dose of either 15 or 30 ml of sodium citrate 0.3 mol litre^{-1}. A further 30 patients who remained unmedicated during labour and required emergency surgery received a preinduction dose of 15 or 30 ml of sodium citrate 0.3 mol litre^{-1} alone. Ranitidine medication resulted in a mean aspirated gastric volume of 31.4 (26.6) ml and pH of 5.3 (2.1); five of 30 patients had a pH < 2.5. The addition of sodium citrate 0.3 mol litre^{-1} resulted in gastric pH > 2.5 in all patients and a mean gastric volume of 43.2 (38.3) ml. The group who received only sodium citrate 0.3 mol litre^{-1} had a mean pH of 5.3 (1.1) and a mean volume 122.7 (98.2) ml.

Aspiration pneumonitis as an obstetric hazard with a fatal outcome was first reported by Charles Hall in 1940 [1], and the syndrome was described and investigated by Curtis Mendelson 6 years later [2]. Anaesthetically-related maternal deaths in England and Wales, reported triennially since 1952, have been most commonly attributed to the aspiration of regurgitated gastric contents, and this mortality has not diminished following the introduction and widespread practice of antacid administration during labour [3–5]. In addition to the acidity [2] of the inhaled gastric contents, their volume [6] and nature [7] have been shown to influence the resulting pulmonary damage.

Since the introduction of the H_2-receptor antagonists, much research has focused on their potential use in the prophylaxis of aspiration pneumonitis [8–14]. At present there is no consensus on the optimum pharmacological regimen for obstetric patients who are electively, or potentially likely, to undergo a procedure requiring anaesthesia, or who are at risk of pulmonary aspiration during CNS depression from other causes. The parenteral route for the administration of the H_2-receptor antagonists would offer the advantage of improved bioavailability in the obstetric situation, when delayed gastric emptying might render oral medication least effective when most required. In addition, the duration of action of 6–8 h following parenteral ranitidine [15], would result in infrequent dosage and minimum invasiveness.

The present study was designed to examine the efficacy of a proposed regimen using ranitidine, initially by mouth and then i.m. every 6 h once labour was established or, in the case of elective surgery, 90 min before anaesthesia. We also wished to investigate the need for the addition of an aqueous antacid (sodium citrate 0.3 mol litre^{-1}) and the minimum dose required to afford the maximum "protection". With the renewed interest in less invasive obstetrics, the concept of universal prophylaxis has been questioned. In this study, prophylaxis was selectively offered to patients considered "at risk", or who became at risk during the course of labour. Should

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emergency surgery become necessary for an unmedicated patient, she would receive a single dose of sodium citrate 0.3 mol litre^{-1}, and here again we wished to re-evaluate the efficacy of a reduced dose [16,17].

PATIENTS AND METHODS

One hundred and ten obstetric patients (ASA I and II) at term were studied: 20 patients underwent elective Caesarean section and 90 parturients required emergency operations during the course of their labour. Elective patients were fasted for a minimum of 8 h. All patients were fasted once labour became established. The technique of analgesia used during labour was noted for each patient, including the drugs administered and the times of their administration.

There were four groups of patients:

Group 1 = 20 elective cases; ranitidine only.
Group 2 = 30 emergency cases; ranitidine only.
Group 3 = 30 emergency cases; ranitidine and sodium citrate.
Group 4 = 30 emergency cases; sodium citrate only.

Elective anaesthesia (group 1)

Patients scheduled for an elective Caesarean section received ranitidine 150 mg by mouth at 22.00 h the night before if surgery was planned in the morning, or at 06.00 h of the same day if surgery was planned in the afternoon. They all received a second dose of ranitidine 50 mg i.m. 90 min before surgery. No sodium citrate was given.

Emergency anaesthesia (groups 2–4)

Patients admitted to the labour ward were selected to commence ranitidine treatment if they:

(a) had undergone a Caesarean section previously, or had had a retained placenta;
(b) were considered "at risk", which was defined as any associated obstetric or medical abnormality, and included those undergoing a trial of labour;
(c) received pethidine or an extradural block;
(d) developed fetal or maternal complications in the course of labour.

If, when selected, the patient was in early labour and still ambulatory, medication commenced with ranitidine 150 mg by mouth and continued with ranitidine 50 mg i.m. 6-hourly. If, however, she was already in established labour, the patient received ranitidine 50 mg i.m., to be repeated 6-hourly (fig. 1).

When those patients who were medicated with ranitidine required general anaesthesia for an emergency Caesarean section, they were randomly

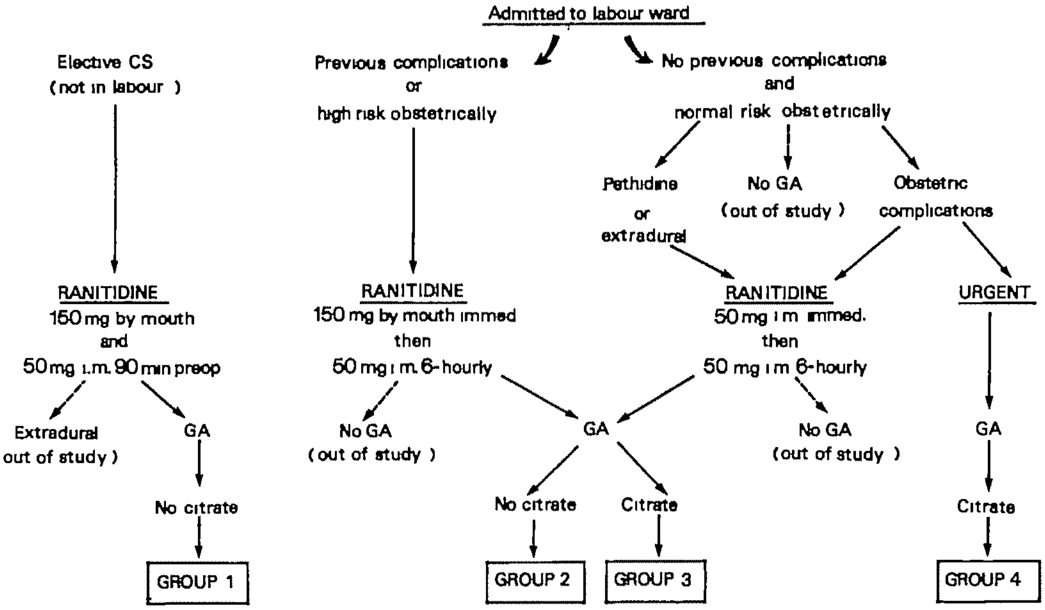
Admitted to labour ward
Elective CS (not in labour)
Previous complications or high risk obstetrically
No previous complications and normal risk obstetrically
Pethidine or extradural
No GA (out of study)
Obstetric complications
RANITIDINE 150 mg by mouth and 50 mg i.m. 90 min preop
RANITIDINE 150 mg by mouth immed then 50 mg i m. 6-hourly
RANITIDINE 50 mg i m immed. then 50 mg i m 6-hourly
URGENT
Extradural (out of study)
GA
No GA (out of study)
GA
No GA (out of study)
GA
No citrate
No citrate
Citrate
Citrate
GROUP 1
GROUP 2
GROUP 3
GROUP 4

FIG. 1. Flow chart of group classifications. CS = Caesarean section; GA = general anaesthesia.

allocated to groups 2 or 3. Group 2 received no sodium citrate; group 3 was subdivided randomly into patients who received either 15 ml or 30 ml of sodium citrate 0.3 mol litre^{-1} in the anaesthetic room immediately before entering the operating theatre.

Patients without ranitidine pretreatment, in whom the urgency of operative intervention precluded such therapy, formed group 4. They all received sodium citrate 0.3 mol litre^{-1}, in either 15-ml or 30-ml randomly allocated doses.

All patients

General anaesthesia was used in all patients. A Crawford's wedge was positioned to provide lateral uterine displacement. The patient was preoxygenated for 3–5 min and cricoid pressure applied. Methohexitone 80–100 mg or thiopentone 250 mg and suxamethonium 100 mg were administered i.v. and tracheal intubation performed. Anaesthesia was maintained with 50 % nitrous oxide in oxygen and 0.5 % halothane until delivery of the infant, when 67 % nitrous oxide in oxygen was used, supplemented with fentanyl 50–200 μg.

Shortly after intubation, a 16-French gauge Salem Sump orogastric tube was passed and the gastric contents aspirated. When no further aspiration was possible, the orogastric tube was withdrawn and reintroduced twice more in an attempt to aspirate any residual contents. The total volume was measured. The pH of the sample was measured within 1 h using a Radiometer 27 pH meter calibrated at pH 4.01 and pH 1.67 before each reading. Student's *t* test for unpaired data and chi-squared test were used for statistical analysis as appropriate.

Neonatal Apgar scores at 1 and 5 min were assessed by the paediatrician and recorded.

RESULTS

General anaesthesia was administered for 20 elective Caesarean sections, 85 emergency Caesarean sections, one cervical laceration and to four patients with a retained placenta. Of the 60 emergency patients treated with ranitidine during labour, 30 % commenced with an oral dose and 70 % with an i.m. dose. Thirty-one patients had one dose of ranitidine only; three of these received the oral medication in early labour and 28 patients one i.m. dose in the course of their labour.

TABLE I. *Maternal age, gestation and duration of labour (mean (SD))*

	Age (yr)	Gestation (weeks)	Labour (h)
Group 1	27.1 (5.1)	39.2 (1.2)	—
Group 2	27.0 (4.4)	38.2 (2.9)	10.2 (8.7)
Group 3	26.3 (4.5)	39.2 (2.5)	10.5 (7.4)
Group 4	26.9 (5.1)	39.3 (2.0)	11.4 (7.8)

There were no statistically significant differences in maternal age, gestation, duration of labour or the fasting interval for patients in the four groups (table I). The mean duration of ranitidine treatment was 11.8 (SD 3.5) h for the scheduled cases (group 1), and 6.7 h for the patients receiving ranitidine during labour (groups 2 and 3). There were no significant differences between groups 2 and 3 for the administration of ranitidine (table II) or pethidine (table III).

Fetal distress as an indication for emergency Caesarean section occurred more frequently in the group of patients who received sodium citrate alone (57 %), compared with patients considered at risk in early labour and pretreated with ranitidine (40 %) or ranitidine and sodium citrate (40 %).

Gastric volumes and pH

The graph plotting co-ordinates of aspirated gastric volume and pH has been divided into four quadrants to define variable risk factors according to the criteria of Roberts and Shirley [6], for purposes of comparison of the efficacy of the different regimens studied (fig. 2). Quadrant I includes patients with aspirated gastric volumes < 25 ml and pH > 2.5, considered least at risk, while quadrant IV represents patients "at maximum risk" with aspirated gastric contents of > 25 ml and pH < 2.5. The larger volumes in

TABLE II. *Ranitidine treatment (mean (SD)) for groups 2 and 3*

	Group 2 ($n = 30$)	Group 3 ($n = 30$)
Duration of medication (h)	7.3 (8.0)	6.0 (5.3)
Ranitidine doses (n)	1.9 (1.2)	1.6 (0.8)
Time in labour before commencing ranitidine (h)	3.3 (4.5)	5.6 (6.0)
Last ranitidine dose to anaesthetic induction interval (h)	2.2 (2.0)	2.0 (1.6)
Patients commencing with an oral dose (n)	10	8
One oral dose only (n)	1	2
One i.m. dose only (n)	14	14

TABLE III. *Details of pethidine treatment of groups 2 and 3*

	Group 2 ($n = 30$)	Group 3 ($n = 30$)
Patients receiving pethidine (%)	46.7	56.7
Total No. of pethidine injections	21	22

quadrant II are likely to increase the risk of aspiration when compared with quadrant I, although the "safe" pH is likely to reduce the development of the acid aspiration syndrome. Quadrant III should not be considered safe since the contents are acid, and the volumes measured are aspirated volumes only and may underestimate the true gastric volume.

Elective anaesthesia

Group 1 (fig. 3). All patients who underwent elective Caesarean section had aspirated gastric volumes < 25 ml and pH > 2.5 (quadrant I). Mean volume was 9.0 (7.2) ml and mean pH was 6.5 (0.8). This was significantly different ($P < 0.001$) from patients in labour who underwent emergency surgery in groups 2, 3 and 4 (table IV).

Emergency Anaesthesia

Group 2: Ranitidine alone (fig. 4). Values for aspirated gastric contents of patients in this group were found in all quadrants, but predominantly in quadrant I (50%) and quadrant II (33%). However, 14% of patients were in quadrant IV, which by definition is associated with the highest risk of Mendelson's syndrome. This was the highest percentage found in all the groups. Comparison of this group (ranitidine alone) with group 4 (sodium citrate alone) showed a significant difference in mean gastric volume (group 2 31.4 ml; group 4 122.7 ml ($P < 0.001$), while the mean pH of 5.3 was similar in the two groups, although five patients in group 2 had a pH < 2.5, compared with only one in group 4.

Group 3: Ranitidine and sodium citrate (fig. 5). Thirteen patients in this group received 15 ml, and 17 patients 30 ml of sodium citrate 0.3 mol litre^{-1} before anaesthesia in addition to ranitidine. In all patients, this resulted in gastric contents with a pH greater than 2.5; 37% of patients were in quadrant I and 63% in quadrant II. The mean pH was 6.0 (1.0), which was significantly greater than that found in groups 2 and 4 ($P < 0.01$). The mean gastric volume was 43.2 (38.3) ml, which was not statistically significantly different from group 2, but was highly significant ($P < 0.001$) when compared with group 4.

Group 4: Sodium citrate alone (fig. 6). In this group, 14 parturients received 15 ml and 16 received 30 ml of sodium citrate 0.3 mol litre^{-1}. Mean gastric volume aspirated from patients in

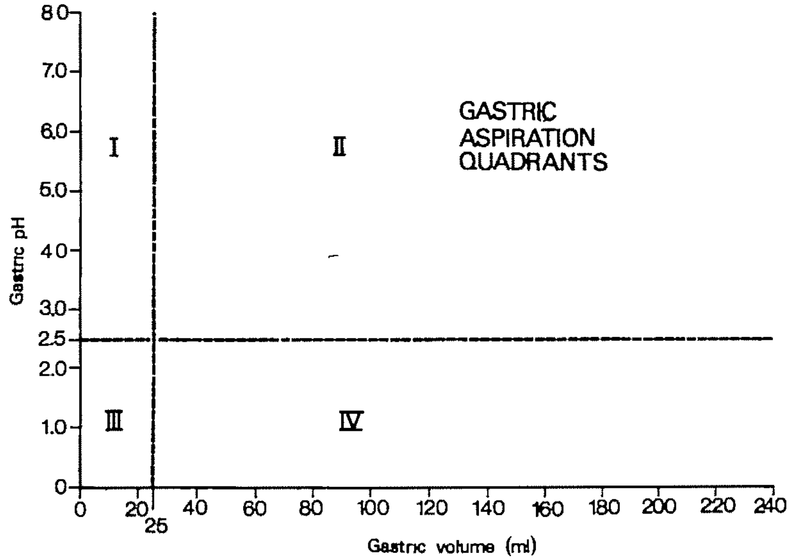

FIG. 2. Division into four quadrants of gastric pH and volume co-ordinates, to indicate "risk" level according to the definition proposed by Roberts and Shirley [6].

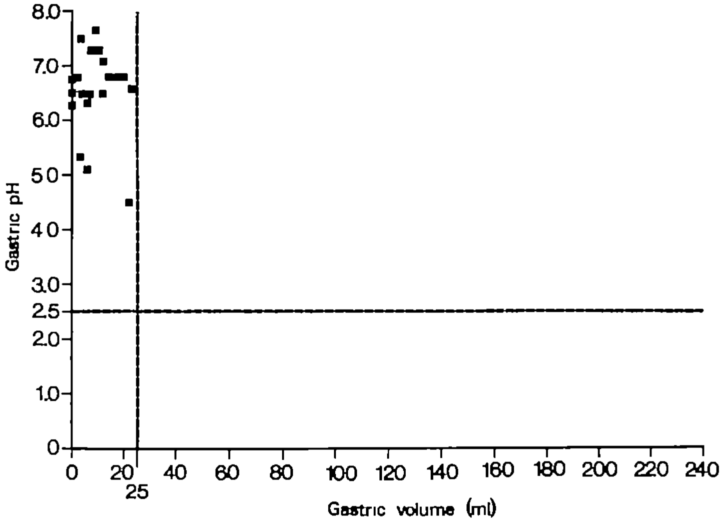

FIG. 3. Group 1: patients who underwent elective Caesarean section and who were premedicated with ranitidine alone.

TABLE IV. *Gastric volume and pH*

		Gastric volume (ml)			Gastric pH		
	n	Mean (SD)	Range	No. > 25 ml	Mean (SD)	Range	No. < 2.5
Group 1	20	9.0 (7.2)	0–23	0	6.5 (0.8)	4.5–7.7	0
Group 2	30	31.4 (26.6)	0–127	14	5.3 (2.1)	1.8–7.7	5
Group 3	30	43.2 (38.3)	4–150	19	6.0 (1.0)	3.9–7.4	0
Group 4	30	122.7 (98.2)	10–450	29	5.3 (1.1)	1.8–7.6	1

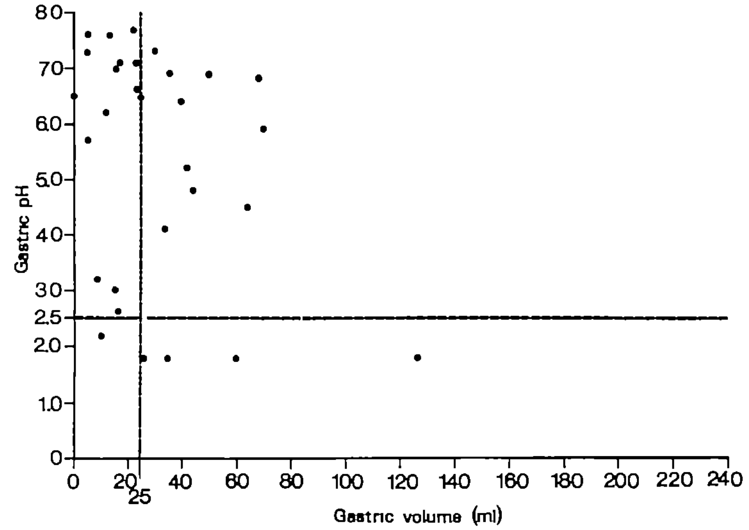

FIG. 4. Group 2: patients who underwent emergency surgery during labour and who were premedicated with ranitidine alone.

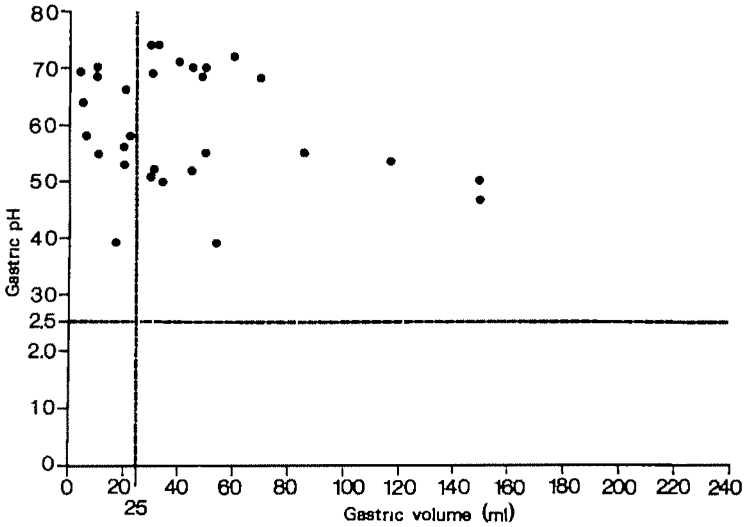

FIG. 5. Group 3: patients who underwent emergency surgery during labour and who were premedicated with ranitidine and sodium citrate 0.3 mol litre^{-1}.

this group, 122.7 (98.2) ml, was significantly greater than that found in the other groups ($P < 0.001$). The mean pH was 5.3 (1.1). Ninety-four percent of patients were in quadrant II. The only patient in quadrant IV had received 15 ml of sodium citrate 0.3 mol litre^{-1}, and had a gastric volume of 450 ml with a pH of 1.8.

Volume of sodium citrate

In group 3 (ranitidine and sodium citrate), there was no statistically significant difference in the mean gastric pH or volume between patients receiving 15 or 30 ml of sodium citrate 0.3 mol litre^{-1}. All patients who received ranitidine and 15 or 30 ml of sodium citrate 0.3 mol litre^{-1} had a gastric pH greater than 2.5. However, in group 4 (sodium citrate alone) there was a significant difference in gastric pH between patients who received 15 ml (pH 4.6 (1.1)) and 30 ml (pH 5.7 (0.8)) of sodium citrate 0.3 mol litre^{-1} ($P < 0.01$), but not in gastric volume. One patient receiving 15 ml of sodium citrate 0.3 mol litre^{-1} had a pH of

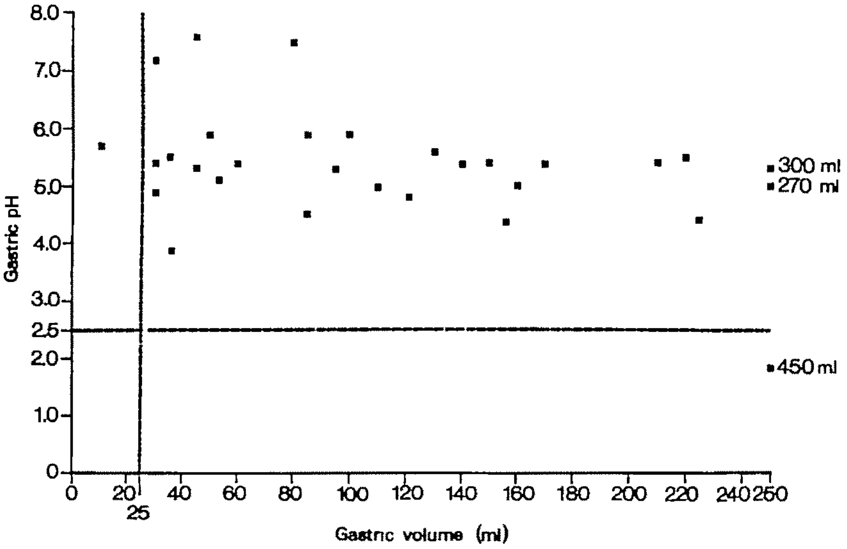

FIG. 6. Group 4: patients who underwent emergency surgery during labour and who were premedicated with sodium citrate 0.3 mol litre^{-1} alone.

TABLE V. *Effects (mean (SD)) of pethidine on volume and pH.* *$^*P < 0.05$*

	No pethidine	Pethidine
Group 2		
n	16	14
Volume (ml)	27.3 (30.02)	36.1 (22)
pH	4.5 (2.4)	6.1 (1.1)*
Group 3		
n	13	17
Volume (ml)	35.5 (29.0)	49.2 (44.0)
pH	5.9 (1.0)	6.0 (1.0)

1.8 (gastric volume 450 ml). All patients receiving 30 ml of sodium citrate had a pH greater than 2.5.

Duration of ranitidine treatment

Neither the number of doses of ranitidine nor the total duration of treatment showed any correlation with gastric volume or pH. Similarly, there was no significant difference between women who commenced ranitidine with an oral dose in early labour or with an i.m. dose in established labour. There was no correlation between the number of hours in labour before commencing ranitidine and gastric pH or volume, nor was there any correlation between the interval from the last dose of ranitidine to the induction of anaesthesia and the gastric pH or volume.

Effect of pethidine

Pethidine was accompanied by promethazine hydrochloride 25 mg i.m. on each occasion. Mean aspirated gastric volume from patients who received pethidine was 43.3 ml, compared with 31.0 ml from patients who received other forms of analgesia, in the group of 60 patients who received ranitidine during labour. This difference did not reach statistical significance.

No difference was found in mean gastric pH in patients in group 3 (ranitidine and sodium citrate) receiving pethidine (pH 6.0) compared with those who did not (pH 5.9). However, in group 2 (ranitidine alone), the mean gastric pH was significantly greater ($P < 0.05$) in the pethidine-treated patients (pH = 6.1) compared with those not receiving pethidine (pH = 4.5) (table V).

TABLE VI. *Neonatal Apgar scores at 1 and 5 min*

	1-min score		5-min score	
	Mean (SD)	Score <6	Mean (SD)	Score <6
Group 1	7.6 (1.9)	20%	9.2 (1.4)	0%
Group 2	6.8 (2.1)	30%	9.0 (1.3)	3%
Group 3	7.1 (2.3)	27%	9.3 (1.0)	0%
Group 4	6.1 (2.2)	33%	8.2 (1.8)	13%

Apgar scores

The 1- and 5-min Apgar scores are listed in table VI. The Apgar scores from the babies in group 4 were lower at both 1 and 5 min, consistent with the higher incidence of preoperative fetal distress in this group (57%), compared with groups 2 (40%) and 3 (40%). Pethidine had no significant effect on the number of babies with a 5-min Apgar score < 6.

DISCUSSION

Efforts at preventing Mendelson's syndrome initially focused on increasing gastric pH above 2.5 with oral antacids administered regularly during labour and before general anaesthesia, but at the expense of increasing gastric volume. The report on Confidential Enquiries into Maternal Deaths in England and Wales 1973–1975 [3] revealed that eight of the nine women who died during that period had received the recommended dose of antacids. In addition, Gibbs and colleagues [7] demonstrated that the instillation of a dilute solution of magnesium trisilicate B.P.C. into the lungs of dogs produced a severe and persistent chemical pneumonitis. Several clinical reports followed, describing severe pulmonary disturbances [18,19] and, in one case, death [5] following the aspiration of gastric contents containing antacids.

Although the volume likely to produce Mendelson's syndrome in man is unknown, Roberts and Shirley [6], proposed that the pulmonary aspiration of greater than 0.4 ml kg^{-1}, or 25 ml in the average parturient, of gastric contents with a pH 2.5 was likely to be hazardous. Use of the more recently introduced H_2-receptor antagonists, cimetidine and ranitidine, has been associated with an increase in pH and a decrease in gastric volume [8–14]. Nevertheless, some patients with a gastric pH < 2.5 have been reported in the studies to date which used an H_2-receptor antagonist. Ranitidine and cimetidine have similar elimination half-lives; however, when using the doses recommended for clinical use it has been found that an increased gastric pH was maintained for 6–8 h following i.m. ranitidine, in contrast to 2–3 h following cimetidine [15]. During labour there is an obvious advantage to the longer interval. Ranitidine also differs chemically from cimetidine, having a furan ring rather than an imidazole ring. Reports have suggested that this difference would leave ranitidine free from competition with the cytochrome P450 enzyme system. Of particular relevance to parturients and neonates may be the prolongation by cimetidine of the metabolism of pethidine, bupivacaine and lignocaine, as well as diazepam, phenytoin, propranolol and warfarin. Studies to date have shown ranitidine to be free from maternal and fetal side-effects [8,9].

During labour, delayed gastric emptying would further slow the absorption of orally administered medication, leaving those patients already at a higher risk from an increased gastric residue, the least protected. Consequently, it was considered worth investigating the regular i.m. route for the administration of ranitidine to patients in labour, and to parturients scheduled to undergo elective surgery, with the view of improving protection against Mendelson's syndrome.

Elective Caesarean section

The combination of oral ranitidine 150 mg at night or in the morning, followed by ranitidine 50 mg i.m. 90 min before operation, resulted in gastric contents within the "safe" limits defined [6] by Roberts and Shirley in all parturients tested.

There are no previous studies using oral and i.m. ranitidine before elective Caesarean section. However, Frank and colleagues [11] studied 16 patients who were pretreated with cimetidine 400 mg by mouth at night or in the morning and cimetidine 200 mg i.m. 90 min before elective Caesarean section. The mean gastric volume was similar to that found in the present study (ranitidine 9.0 ml, cimetidine 10.0 ml), but the range of volumes was larger following cimetidine (0.5–39 ml) than after ranitidine (0–23 ml). The mean gastric pH found in the two studies was similar (ranitidine pH 6.5, cimetidine pH 6.2), but the range was again wider following cimetidine (pH 1.6–7.3) than ranitidine (pH 4.5–7.7). In addition, three patients pretreated with cimetidine had a gastric pH < 2.5.

Two recent studies have assessed a single dose of ranitidine 150 mg by mouth before elective Caesarean section. McAuley and co-workers [8] reported the results following the administration of ranitidine 150 mg by mouth to 80 women undergoing elective Caesarean section at times ranging from 75 to 510 min before surgery. The mean gastric volume was 8.0 (SD 8.0) ml and 3% of patients had a volume > 25 ml. When gastric contents were aspirated 2–6 h after medication, the pH was > 2.5 in all but one patient. Thompson and associates [12] administered ranitidine 150 mg by mouth to 43 patients at least 2 h before operation. The mean gastric volume was 7.7 (SEM 0.15) ml (range 0.5–40 ml), and mean pH was 6.6 (SEM 0.15) (range 3.1–8.2).

O'Sullivan and colleagues [13], found a mean gastric volume of 5 ml (range 2–44 ml) in eight patients receiving ranitidine 150 mg by mouth at 22.00 h and again 2–4 h before elective Caesarean section. The addition of metoclopramide 10 mg i.m. 1–2 h before the operation in a further eight patients resulted in a narrower range of gastric volumes: 2–13 ml. Gastric pH was > 2.5 in all cases, in both groups. These results are comparable to those of the present study. In both cases an initial oral dose of ranitidine was followed by i.m. medication, of metoclopramide or ranitidine, respectively. If these results are maintained in larger series, the additional safety against Mendelson's syndrome provided by an i.m. injection before elective Caesarean section would make this route of administration justified.

The administration of an oral antacid before elective Caesarean section to parturients protected by the proposed regimen of oral and i.m. ranitidine may be unnecessary, according to these results, and would increase gastric volume. Price and Sanderson [20] demonstrated a six- to 20-fold increase in intragastric hydrogen ion concentration following antacids. Thompson and co-workers [12] found the addition of sodium citrate 0.3 mol litre^{-1} increased mean gastric volume from 7.7 ml (range 0.5–40 ml) to 28.2 ml (range 0.5–90 ml), and Gillett and colleagues [10], using ranitidine by mouth, metoclopramide 10 mg i.m. and sodium citrate 0.3 mol litre^{-1} reported a mean gastric volume of 45.2 ml (range 6–150 ml).

Emergency anaesthesia

We wished to investigate the efficacy of a regimen of i.m. ranitidine 50 mg 6-hourly during labour (following an initial oral dose of 150 mg if medication started before established labour) as the sole pharmacological prophylaxis against aspiration pneumonitis in the event of emergency surgery and if, were it necessary, the reduced dose of 15 ml of sodium citrate 0.3 mol litre^{-1} was as effective as the commonly recommended dose of

30 ml in this group of patients. Previous studies [16,17] suggested that the reduced dose of sodium citrate 0.3 mol litre^{-1} was associated with an increase in gastric pH similar to that found following the larger dose, although the duration of action was shorter. Ranitidine alone was associated with a highly significant reduction in gastric volume compared with the unmedicated group ($P < 0.001$), but five of the 30 patients had a gastric pH < 2.5. In four of these patients, the gastric volume was > 25 ml, placing the patients "at risk".

The addition of either 15 or 30 ml of sodium citrate 0.3 mol litre^{-1} resulted in gastric pH values greater than 2.5 in all our patients (range pH 3.9–7.4), and there was no statistically significant difference in either gastric pH or volume following the administration of 15 or 30 ml of the antacid in the ranitidine-treated patients. However, mean gastric volume was higher (ranitidine alone: mean volume 31.4 (26.6) ml; ranitidine and sodium citrate: mean volume 43.2 (38.3) ml), although this difference did not reach statistical significance.

The larger gastric volumes in our group of patients who received sodium citrate 0.3 mol litre^{-1} alone (mean volume 122.7 (98.2) ml) was associated with the failure, following the administration of the reduced dose, to increase gastric pH above 2.5 in one patient who had a gastric volume of 450 ml. The mean gastric volume was unaffected by the choice of 15 or 30 ml of antacid in this group, although the mean gastric pH after 15 ml of antacid (pH 4.6) was significantly ($P < 0.01$) lower than after 30 ml (pH 5.7).

The above results indicate that the 6-hourly i.m. ranitidine regimen cannot be relied on as sole prophylaxis against aspiration pneumonitis. Combined with either 15 or 30 ml of sodium citrate 0.3 mol litre^{-1} given immediately before induction of anaesthesia, the ranitidine medication was consistently associated with "safe" gastric contents as regards pH and volume. However, the reduced dose of 15 ml of sodium citrate was not adequate protection in patients who had not received ranitidine medication.

Regimens using oral ranitidine during labour have been reported. McCauley and co-workers [9], in a study of 51 patients undergoing emergency Caesarean section and pretreated with ranitidine 150 mg by mouth 6-hourly during labour, found their mean gastric volume was 83 ml (range 1–472 ml). The pH was < 2.5 in four patients. Thompson and colleagues [12] studied 103 women undergoing emergency Caesarean section. In addition to ranitidine 6-hourly by mouth during labour, they received a preinduction dose of 30 ml of sodium citrate 0.3 mol litre^{-1}. The pH was greater than 2.5 in all but one patient (mean pH 6.2, range 2.1–8.4). The mean gastric volume in Thompson's group was 70.2 ml (range 0.5–872 ml). Gillett and associates [10] studied 99 patients who, in addition to ranitidine 150 mg by mouth 6-hourly during labour and 30 ml of sodium citrate 0.3 mol litre^{-1} before the induction of anaesthesia, were given metoclopramide 10 mg i.m. as soon as the decision to operate was made. All patients had a gastric pH > 2.5 (mean 6.3). The mean gastric volume was 50.8 ml (range 4–140 ml). These results are comparable to those obtained from the group of patients in the present study who received ranitidine 50 mg i.m. 6-hourly during labour and the full dose (30 ml) of sodium citrate 30 mol litre^{-1} before anaesthesia (mean gastric pH 6.3, range 3.9–7.2; mean gastric volume 39.8 ml, range 5–150 ml). However, previous work by Nimmo and colleagues [21] suggested that the inhibitory effect of pethidine on gastric emptying is not antagonized by metoclopramide.

In conclusion, ranitidine treatment was not associated with any evident maternal or neonatal adverse effects. For elective Caesarean section the combination of ranitidine 150 mg by mouth at night or in the morning and ranitidine 50 mg i.m. 90 min before operation consistently resulted in gastric contents within the defined "safe" limits. For emergency surgery in the course of labour, pretreatment with 6-hourly i.m. ranitidine alone resulted in a gastric pH < 2.5 in 17% of patients, despite a highly significant reduction in the mean gastric volume compared with an untreated group. The addition of the reduced dose of 15 ml of sodium citrate 0.3 mol litre^{-1} resulted in a gastric pH greater than 2.5 in all the patients studied. However, emergency patients not pretreated with ranitidine were better protected with a preanaesthetic dose of 30 ml of sodium citrate 0.3 mol litre^{-1}. The premedication regimens under discussion are additional to the standard recommended practices in the prophylaxis of Mendelson's syndrome, which include a rapid sequence i.v. induction in association with Sellick's manoeuvre if general anaesthesia is required, and the judicious use of regional analgesia where possible.

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INCREASED VENTILATION REQUIREMENTS DURING OBSTETRIC GENERAL ANAESTHESIA

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SUMMARY

The inspiratory fresh gas flow rate (FGF) required to produce an end-tidal carbon dioxide tension (PE'_{CO_2}) of 4 kPa during general anaesthesia, neuromuscular blockade and artificial ventilation, was compared in a group of 46 obstetric patients and a matched group of 50 non-pregnant female patients. The non-pregnant patients required a mean (SD) inspiratory FGF of 77 (10.6) ml kg^{-1} min^{-1}, whereas the pregnant patients required a mean FGF of 121 (24.6) ml kg^{-1} min^{-1} before delivery (in those who reached a stable state), and 109 (19.3) ml kg^{-1} min^{-1} after delivery. These represent significant ($P < 0.0001$) increases of 57% and 42%, respectively, over the non-pregnant state.

During pregnancy metabolic rate and carbon dioxide production increase by 30–33% [1–3]. In addition, hyperventilation occurs, causing a reduction in arterial carbon dioxide tension (Pa_{CO_2}) to 3.9–4.2 kPa [4–6]. These effects are present by 12 weeks gestation, possibly having begun within days of conception. Both these factors produce an increase in the awake resting minute volume of the pregnant patient of between 42% and 57% [1–4]. Much more marked hyperventilation can occur during labour. These metabolic and respiratory changes persist for 2–14 days post-partum [1,2,5].

Much has been written as to the possible beneficial or detrimental effects on the fetus of hypercapnoea and hypocapnoea, both during labour and during general anaesthesia for operative delivery. However, it is now generally accepted that it is probably best to try and reproduce the physiological carbon dioxide tension of 4 kPa.

Although the physiological changes in metabolism and ventilation that occur during pregnancy are widely appreciated, until recently little has been published on determining how large an increase in ventilation is required during obstetric general anaesthesia. This study was undertaken to determine what increase in inspiratory fresh gas flow (FGF) is required in pregnant patients, during general anaesthesia (associated with neuromuscular blockade and artificial ventilation) to produce a carbon dioxide tension of 4 kPa. Since metabolic rate is related to age and sex in addition to body mass [7], a group of obstetric patients was compared with a group of non-pregnant female patients of a similar age range, undergoing gynaecological surgery. End-tidal expired carbon dioxide tension (PE'_{CO_2}) was used as an indicator of Pa_{CO_2}.

PATIENTS AND METHODS

Patients

The obstetric patient group comprised 46 patients having elective or emergency operative delivery under general anaesthesia, the majority having Caesarean section, a small proportion having forceps delivery. The non-pregnant patient group comprised 50 female patients aged up to 45 yr, receiving general anaesthesia for elective gynaecological surgery. Patients were excluded if they had any symptoms or clinical evidence of cardiovascular, respiratory or metabolic disease, and if they were febrile.

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Anaesthetic technique

The anaesthetic technique for the obstetric patients consisted of premedication with antacid only, pre-oxygenation, cricoid pressure and rapid sequence induction with thiopentone i.v. Suxamethonium was administered and, after intubation of the trachea, anaesthesia was maintained until delivery with 50% nitrous oxide and 0.5% halothane in oxygen. Atracurium was given to provide muscle paralysis. After delivery the halothane was discontinued, the nitrous oxide concentration was increased to 70%, and an opioid was administered i.v. The non-obstetric patients were all premedicated with papaveretum and hyoscine, and received thiopentone, fentanyl and atracurium at induction of anaesthesia, which was maintained with 70% nitrous oxide and 0.5% halothane or 1.0% enflurane in oxygen.

The ventilator used for all patients was a Medishield Manley Pulmovent MPP with a standard black rubber patient breathing system. The volume of the breathing system and catheter mount was 1025 ml by water displacement. Tidal volumes (as measured by a Wright's respirometer) were adjusted to between 10 and 15 ml kg^{-1} up to a maximum of 1000 ml. Maximum airway pressures measured by the gauge on the ventilator ranged from 18 to 24 cm H_2O for all the patients studied. The obstetric patients had a 15° left lateral tilt before delivery and were supine after delivery. The gynaecological patients were supine at the time that the ventilatory measurements were made.

Ventilatory measurements

$P\text{E}'_{CO_2}$ was measured using a Datex CD102 capnograph, sampling from the centre of an adaptor mounted on the tracheal tube connector, at a flow rate of 50 ml min^{-1}. For the first 50 patients, the capnograph was zeroed and calibrated (using Datex calibration gas) for every patient. The capnograph proved to be very stable and, subsequently, was re-zeroed for every patient but only recalibrated at intervals. In all patients the rotameter flow rates were adjusted until a stable $P\text{E}'_{CO_2}$ of 4 kPa was obtained. In order to obtain a stable value during the induction to delivery period in the obstetric patients, this sometimes required adjustment of the flow rate every 1–2 min. In the non-pregnant patients, and after delivery in the obstetric patients, there was little problem achieving a steady state, and flow rate recordings were made towards the end of the surgical procedure.

Considerable time was spent on selecting a method for measuring the required FGF. A technique was needed which would give a steady flow rate reading from the pulsatile flow output from the ventilator. In addition, it was necessary to obtain readings in a short period for the frequently unstable pre-delivery values. Use of a pneumotachograph was excluded because of the long warm up time required (50% of the obstetric patients were having unplanned emergency procedures). Attempts to measure cumulative inspiratory gas volume over precisely timed intervals using mechanical and electronic Wright's respirometers and a Drager volumeter gave very inaccurate results, probably as a result of the rapid initial flow rate at the onset of the inspiratory phase. In addition, this method was sometimes impractical, with frequently adjusted flow rates in the period before delivery in the obstetric patients.

Eventually, it was decided that during each anaesthetic we would simply record the flow rate readings from the rotameters at the point when $P\text{E}'_{CO_2}$ was stable at 4.0 kPa. In addition, at intervals during the study we assessed the accuracy of the rotameters and confirmed that there were no leaks in the anaesthetic machines, ventilators and breathing systems that were used. Subsequently, we also determined and applied correction factors for the errors from ventilator back pressure and compliance of the ventilator and its circuit.

The accuracy of the rotameters was assessed at intervals during the study over the range of 4–14 litre min^{-1} of 50% nitrous oxide in oxygen by comparing their flow rates (with no back pressure applied) against those from a regularly calibrated GEC Elliot 1100 reference rotameter. Testing for leaks at similar intervals excluded any greater than 250 ml min^{-1}. Determination of correction factors for the two errors mentioned above was performed using a Mercury Electronics CS5 pneumotachograph connected to a Gould MK220 chart recorder. Error from back pressure was determined by comparing flow rates at the common gas outlet for a constant rotameter setting with and without ventilator back pressure applied. Errors from compliance were determined by comparing gas flow at the input to the ventilator with those at the distal end of the catheter mount, both with patients and with a Medishield Lung Simulator (using a range of tidal volumes of

500–1000 ml and a range of lung compliances of 50–20 ml (cm $H_2O)^{-1}$. These determinations of the necessary correction factors were repeated on three occasions, using gas flows of 4, 6, 8, 10, 12 and 14 litre min^{-1}. The required correction factors were obtained from the ratio of the slopes of cumulative volume against time (thus converting any pulsatile flow to a constant value). No attempt has been made to adjust for variations in ambient pressure or temperature, gas sampling or the addition of the inhalation agent.

With the prior verbal consent of eight of the obstetric patients, a single arterial blood sample (radial artery) was taken at a point when $P\text{E}'_{CO_2}$ was stable, to determine the arterial to end-tidal carbon dioxide tension gradient ($Pa_{CO_2}-P\text{E}'_{CO_2}$).

Analysis of results

Linear regression equations were derived for the correction factors for back pressure on the rotameters and the compliance of the ventilator and breathing system. Linear regression and correlation analyses were performed for the FGF results against the patients' age, weight, height and body surface area. Statistical comparisons between groups were performed using Student's paired or unpaired *t* test as appropriate.

RESULTS

Details of the patients are given in table I. Body surface area was estimated from a standard nomogram [7] (possibly inappropriate for pregnant patients). There were no significant differences between the two groups ($P > 0.05$) for age, height, weight and estimated body surface area (using the weight of the obstetric patients at the time of the first ante-natal visit).

The $Pa_{CO_2}-P\text{E}'_{CO_2}$ gradient measurements in eight obstetric patients showed a mean value of 0.09 kPa (range −0.16 to +0.36 kPa).

TABLE I. *Demographic data for the patients studied. Mean (SD)*

	Obstetric patients ($n = 46$)	Non-pregnant patients ($n = 50$)
Age (yr)	30.4 (7.0)	33.0 (6.4)
Height (m)	1.60 (0.07)	1.62 (0.07)
Weight (kg)		
At operation	71.0 (15.0)	64.2 (10.8)
At first ante-natal visit	61.6 (14.0)	
Estimated surface area (m^2)	1.73 (0.19)	1.68 (0.13)
Gestation (weeks)	37.1 (4.1)	
Number in labour	23 (50%)	

Assessment of accuracy of the rotameters on all the anaesthetic machines used showed mean (SD) errors of −1.6 (2.6)% with a range of −5.1% to +3.6%. No correction has been made for these errors, since they were randomly spread around a mean of near zero. Assessment of rotameter under-reading as a result of back pressure gave a regression equation of: Actual gas flow = rotameter reading × (1.028 + rotameter reading × 0.00077); thus rotameter under-reading ranged from 3.1% at 4 litre min^{-1} to 3.9% at 14 litre min^{-1}. These figures are slightly lower than the theoretically predicted values (the back pressure from a Manley Pulmovent MPP varies from approximately 85 mm Hg at 4 litre min^{-1} to 120 mm Hg at 14 litre min^{-1}). Assessment of gas loss in the ventilator and its circuit gave a regression equation of: Actual inspiratory gas flow = FGF to ventilator × (0.963 − FGF to ventilator × 0.0082), thus giving a gas loss which ranged from 7.0% at 4 litre min^{-1} to 15.2% at 14 litre min^{-1}. All the FGF quoted below are the values after correction with these two regression equations.

Figures 1 and 2 show scatter plots for the FGF results against body weight and estimated body surface area, respectively. Correlation coefficients for the FGF results against age, height, weight and estimated body surface area were 0.11, 0.49, 0.55 and 0.57, respectively, for the post-delivery values in the obstetric patients, and 0.01, 0.20, 0.57 and 0.58, respectively, in the non-pregnant patients. Thus age and height are very poor predictors of the required FGF, weight and body surface area being considerably better. Since body surface area may not always be available to the anaesthetist, the only FGF rates discussed subsequently are those expressed in terms of ml kg^{-1} min^{-1}.

The mean FGF results for each group are given in table II. The mean FGF rate in the non-pregnant patients was 77 ml kg^{-1} min^{-1}, and in the obstetric patients after delivery was 109 ml kg^{-1} min^{-1}. In 30 of the 46 obstetric patients a roughly stable pre-delivery mean value of 121 ml kg^{-1} min^{-1} was obtained—12 ml kg^{-1} min^{-1} greater than the values after delivery in the same 30 patients. Both pre- and post-delivery minute volumes were significantly different from those for the non-pregnant patients ($P < 0.0001$). The spread of results was slightly greater for the obstetric patients.

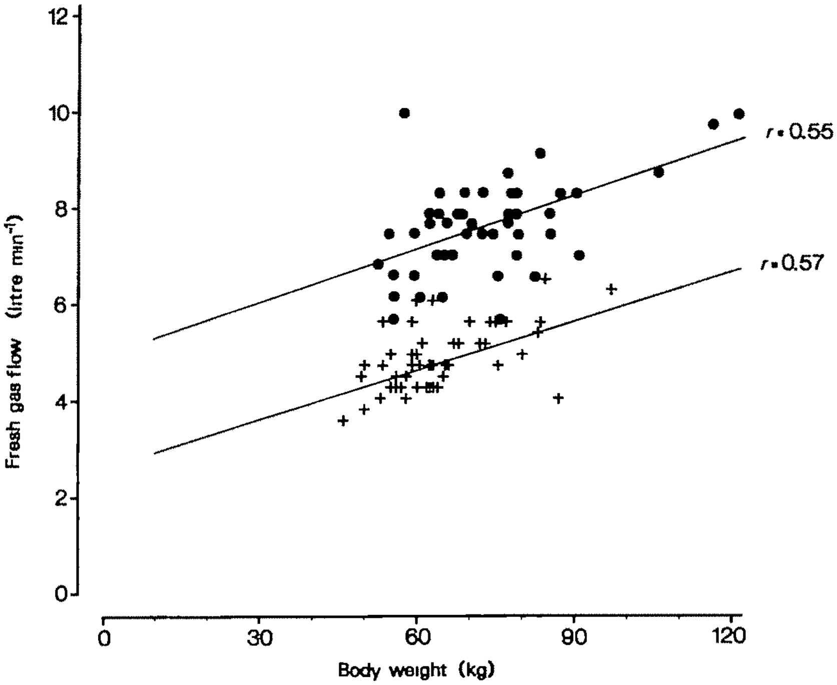

FIG. 1. Inspiratory fresh gas flows required for an end-tidal carbon dioxide tension of 4 kPa in relation to body weight, with lines of best fit and correlation coefficients. ● = Obstetric patients (using post-delivery values); + = non-pregnant patients.

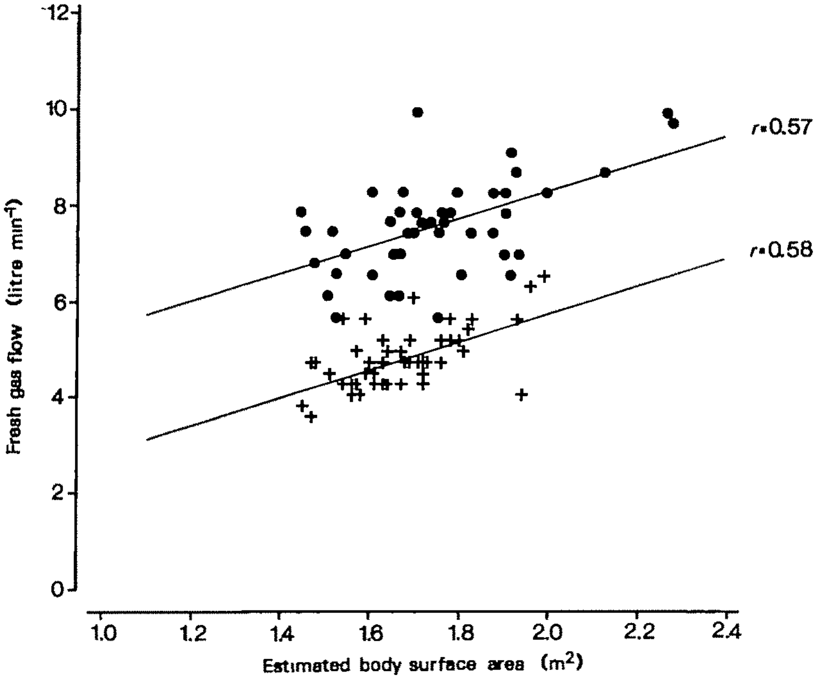

FIG. 2. Inspiratory fresh gas flows required for an end-tidal carbon dioxide tension of 4 kPa in relation to estimated body surface area, with lines of best fit and correlation coefficients. ● = Obstetric patients (using post-delivery values); + = non-pregnant patients.

TABLE II. *Fresh gas flow rates required for an end-tidal carbon dioxide of 4 kPa. Mean (SD)*

	Fresh gas flow rates		
	Absolute (litre min^{-1})	Per unit weight (ml kg^{-1} min^{-1})	Per unit area (litre m^{-2} min^{-1})
Non-pregnant ($n = 50$)	4.88 (0.66)	77.1 (10.6)	2.91 (0.32)
Pregnant			
Before delivery ($n = 30$)	8.47 (1.35)	121.4 (24.6)	4.86 (0.69)
After delivery ($n = 46$)	7.57 (1.00)	109.4 (19.3)	4.39 (0.51)

The difference in FGF requirement in the obstetric patients between those in labour (mean 107 ml kg^{-1} min^{-1}) and those not in labour (mean 112 ml kg^{-1} min^{-1}) was not significant ($P > 0.2$). Figure 3 shows the FGF results (in ml kg^{-1} min^{-1}) plotted against gestation, there being no significant relationship ($r = -0.29$).

DISCUSSION

Study design

Our study was meant to provide guidelines for appropriate FGF requirements during a technique of obstetric general anaesthesia, including neuromuscular blockade and artificial ventilation. In the normal clinical circumstances carbon dioxide tensions will not be stable during the induction-to-delivery interval, particularly when the need for delivery is urgent. However, this is the important period during which alteration of the mother's respiratory indices may influence the condition of the fetus. Extending the induction-to-delivery interval would have enabled more precise estimation of the FGF requirements at this time; however, this would probably be ethically unacceptable, and the results obtained would be less relevant to the clinical circumstances.

Our method of measurement of the FGF rates, involving recording of rotameter settings then

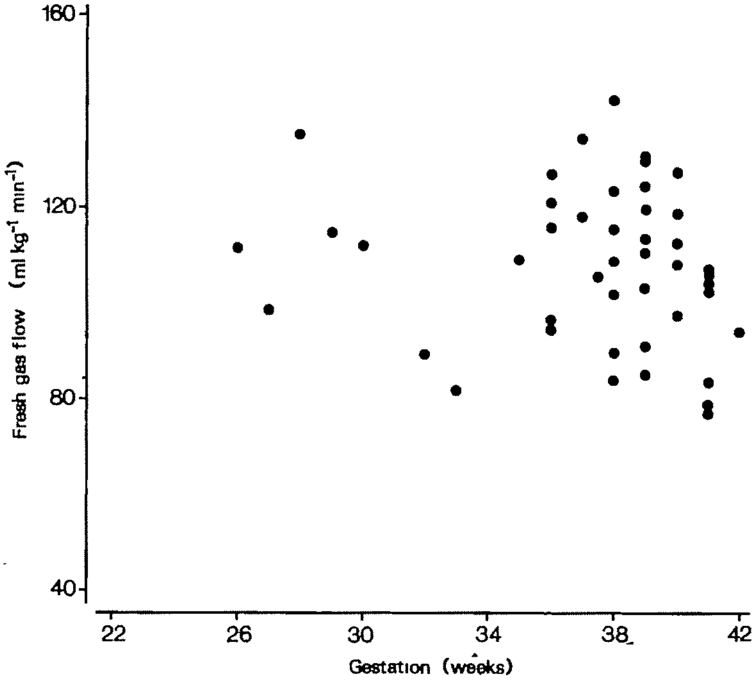

FIG. 3. Inspiratory fresh gas flows required for an end-tidal carbon dioxide tension of 4 kPa in relation to gestation in the obstetric patients, using post-delivery values ($r = -0.29$).

applying subsequent correction factors, was rather indirect. Ideally, the inspiratory FGF would have been precisely measured at a point near the patient at the time when $P\text{E}'_{CO_2}$ was stable at 4.0 kPa. However, this was found to be unrealistic, for the reasons stated earlier. In practice, the rotameters remained accurate throughout the study and the correction factors were stable on repeated estimation. We feel that any errors in the measurement system are insignificant compared with both the inter-individual variation and the difference between the obstetric and non-obstetric groups.

Arterial to end-tidal CO_2 gradients

The $Pa_{CO_2}-P\text{E}'_{CO_2}$ gradient in eight obstetric patients was very low, with a mean value of 0.09 kPa. The expected value in non-pregnant anaesthetized patients is of the order of 0.2–0.6 kPa. Situations with increased pulmonary blood flow and ventilation (for example in exercising patients) can produce a negative Pa_{CO_2}–$P\text{E}'_{CO_2}$ gradient [8]; thus these factors may have contributed to the low gradient we found. Since this study was undertaken, another report of Pa_{CO_2}–$P\text{E}'_{CO_2}$ gradients during general anaesthesia for Caesarean section has been published [9]. This showed a mean gradient of 0.004 kPa before delivery (with negative gradients in 43 % of the patients), and 0.10 kPa after delivery. Another study [10] showed a mean negative gradient of 0.09 kPa. Thus it would appear that $P\text{E}'_{CO_2}$ is a very good indicator of Pa_{CO_2} in anaesthetized and ventilated obstetric patients.

Fresh gas flow rates

Our study shows that pregnancy produces a very significant increase in the FGF necessary to produce a carbon dioxide tension of 4.0 kPa during general anaesthesia, with 121 and 109 ml kg^{-1} min^{-1} being required in the periods before and after delivery, respectively, representing increases of 57 % and 42 % over those required in non-pregnant patients. In our study roughly stable pre-delivery results were obtained in 30 patients. In practice the half-time required for Pa_{CO_2} to stabilize after a change in ventilation is 3–4 min for an increase in ventilation, and 15–20 min for a reduction in ventilation [11]. The induction-to-delivery time in the majority of our patients was between 5 and 10 min, thus attempts to obtain an absolutely steady state before delivery are not realistic. The pre-delivery results, where obtained, were slightly higher than those seen after delivery. Although the metabolic demands of the fetus and placenta cease at delivery, there are additional possible reasons for the higher value before delivery. The transient apnoea at induction, stimulation at intubation, and light level of anaesthesia will all contribute to higher carbon dioxide tensions at the onset of the procedure. We found no significant difference in FGF requirements between patients in labour and those not in labour.

As mentioned earlier, the metabolic and ventilatory changes induced by pregnancy take from 2 to 14 days to resolve post-partum. Thus anaesthesia early in the post-partum period will still require these increased FGF rates.

Other workers who have attempted to determine FGF requirements during obstetric general anaesthesia have divided patients into separate groups allocated to receive different predetermined FGF rates throughout the procedure. Kneeshaw, Harvey and Thomas [12] allocated 26 patients undergoing Caesarean section to groups ventilated with 80, 100, or 120 ml kg^{-1} min^{-1} using a Bain breathing system and Penlon Oxford ventilator. They measured $P\text{E}'_{CO_2}$ and claimed that stable values were obtained before delivery in all patients. They did not state how FGF was measured. They found that, with the greatest FGF the mean $P\text{E}'_{CO_2}$ before delivery was 4.2 kPa. Duncan and colleagues [13] allocated 32 patients undergoing Caesarean section to receive FGF of 70 or 100 ml kg^{-1} min^{-1}, using a Humphrey (ADE) circuit and a Penlon 200 ventilator. They did not state how FGF was estimated, although the tidal volume was recorded with a Wright's respirometer. They found that the mean $P\text{E}'_{CO_2}$ using 100 ml kg^{-1} min^{-1} was 4.9 kPa and stated that a flow greater than this would be required to prevent carbon dioxide values increasing above the pre-induction values. They found that, in the group with the lower FGF, the $P\text{E}'_{CO_2}$ had not reached a stable value even by the end of the procedure. Burger and colleagues [10] allocated 18 patients undergoing Caesarean section to receive FGF of 80, 90 or 100 ml kg^{-1} min^{-1} using a volume-cycled ventilator, measuring Pa_{CO_2} and $P\text{E}'_{CO_2}$, and measuring expired gas flow with a Drager Volumeter. They found, using the highest flow rate, that the mean Pa_{CO_2} at the time of delivery was 4.2 kPa. Thus none of these three groups managed to obtain mean carbon dioxide tensions quite as low as 4.0 kPa, despite using claimed FGF of 100–120 ml kg^{-1} min^{-1}. Two of the three did not state how the FGF was measured or estimated, and the third used a Drager Volumeter on the expiratory limb, a method which in our experience gave marked overreading. None used the same measurement system in non-pregnant patients for comparison.

The clinical importance of carbon dioxide tension

Alterations in maternal carbon dioxide tension are important because of their possible effects on fetal wellbeing, rather than effects on the mother. Altering maternal carbon dioxide tensions may affect fetal conditions either by effects on uterine blood flow and gas exchange, or by changes in vascular resistance, acid–base balance and oxygen dissociation in the fetus. In addition, mechanical ventilation may affect uterine blood flow regardless of the maternal carbon dioxide tension. Both induced hypocapnoea (in the hope of reversing fetal acidosis) and induced hypercapnoea (intended to increase fetal blood flow and improve oxygen dissociation) have been recommended in the past.

Much of the work that has shown detrimental effects of hyperventilation has been in anaesthetized animals. A study in guineapigs [14] showed significant worsening of fetal pH with hyperventilation, although these animals were markedly hypotensive. Another often quoted study [15], using sheep, found worsening of fetal pH and oxygen tension during hypocapnoeic hyperventilation, but with normocapnoeic hyperventilation having no effect. A further study in sheep [16] showed that maternal hypocarbia produced higher fetal pH, but decreased fetal oxygen tensions, and showed that mechanical ventilation alone reduced uterine blood flow.

All but one of the clinical studies performed during general anaesthesia for Caesarean section have shown that fetal pH and P_{CO_2} always change in the same direction as the changes in the mother [10,17–21]. This is despite gross hyperventilation to a maternal Pa_{CO_2} of less than 2.0 kPa in some of the studies [18,21]. In one study [22] fetal pH did decrease in the group with the most severe maternal hyperventilation, in whom the mean Pa_{CO_2} was 1.8 kPa, assumedly as a result of reduced fetal perfusion. Studies attempting to determine whether umbilical vein P_{O_2} is reduced if maternal Pa_{CO_2} is decreased have given variable results, two showing no relationship [10,21], and two demonstrating a significant relationship [17,20], with one showing no clinical effects [20] and one showing a worse 1-min Apgar score in the neonates from the hyperventilated mothers [17]. Maternal hypercapnoea has been induced in two studies in anaesthetized humans, one showing improvement in umbilical vein oxygen tension but not saturation [23], the other showing increased fetal perfusion, but with very variable effects on fetal acid–base status [24].

Thus all these studies give rather mixed opinions on the ideal maternal Pa_{CO_2}. However, at present, it is increasingly recommended that, during anaesthesia for operative delivery, one should aim to maintain the physiological Pa_{CO_2} of 4 kPa.

In conclusion, we believe that obstetric general anaesthesia is one of the circumstances in which end-tidal carbon dioxide monitoring is of particular benefit and recommend that, to achieve the normal obstetric carbon dioxide tension of 4 kPa, inspiratory fresh gas flow rates of 109–121 ml kg^{-1} min^{-1} be used.

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A TIME AND MOTION STUDY OF THE ANAESTHETIST'S INTRAOPERATIVE TIME

J. S. McDONALD AND R. R. DZWONCZYK

SUMMARY

A time and motion study was made of anaesthetists during 32 surgical procedures. Thirteen activities performed by the anaesthetist were defined for the study. Time and event data were recorded electronically and analysed by digital computer. Activity and link analysis techniques were used to analyse the data. Only 25% of intraoperative time was spent observing the physiological state of the patient. Seventy-five percent was spent in secondary or indirect activities. Direct observation of the patient was least in the middle of the procedure when the anaesthetist was performing secondary activities. Prudent use of personnel, machines, or both, to perform activities not requiring full medical knowledge and training should increase the anaesthetist's ability to focus full attention on the state of the patient and may improve patient care.

In the past 14 years, three systematic time and motion studies have been undertaken on the activities of the anaesthetist in the operating room [1–3]. These studies showed that the anaesthetist spends most time performing tasks that are either secondary or unrelated to immediate care of the patient.

The existence of a non-routine "do it as you think of it" priority was undoubtedly appropriate 30 years ago when monitoring involved only measurement of heart rate and arterial pressure. Today the anaesthetist is faced with both multiple monitoring requirements and complex therapeutic activities. There are no data, however, to suggest that the present complex monitoring systems have had any beneficial effect on anaesthetic accidents. It may be that the increased complexity of monitoring is a distraction and only adds to, rather than lessens, the burden of the anaesthetist. We have re-evaluated intraoperative activities in order to determine if new equipment or new anaesthetic techniques have resulted in any improvement in direct patient-related activities.

MATERIALS AND METHODS

A time and motion study was made of the intraoperative activities of anaesthetists during 32 surgical procedures at The Ohio State University Hospitals from February to May 1981. The study involved mostly residents and several certified registered nurse anaesthetists (CRNA). No resident or CRNA was studied more than once. Procedures lasted from 0.47 to 4.47 h (mean 1.35 (SD 0.85) h). Most of the cases involved gynaecological procedures; the others comprised a Heller procedure, implant removal, renal biopsy, Marshall–Marchetti procedure and correction of toe deformity. All patients were ASA I or II physical status.

The anaesthesia machine, anaesthetic drug trolley and operating table were arranged around, and approximately equidistant from, the anaesthetist. Monitoring equipment was located on or adjacent to the anaesthesia machine. The ventilator was attached to the anaesthesia machine.

Information gathering

The activities studied were all those performed by the anaesthetist during the entire intraoperative period (table I). A single direct patient activity was defined and included all activities during which the anaesthetist had contact with the patient and a view of the surgical field.

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TABLE I. *The 13 intraoperative activities of the anaesthetist and their relationship to the patient*

Patient activities		
Direct	Indirect	Non-patient
(1) Direct patient activities	(2) Observe arterial pressure	(8) Complete patient records
(a) Observe skin colour and capillary refill	(3) Observe ECG	(9) Adjust surgical table
(b) Palpate pulse and skin temperature	(4) Observe or adjust anaesthesia machine	(10) Activity at drug trolley
(c) Listen to breath and heart sounds	(5) Observe, adjust or change i.v. infusions	(11) Communication, non-patient related
	(6) Perform peripheral nerve stimulation	(12) Idle time
	(7) Observe circle system	(13) Unclassified time

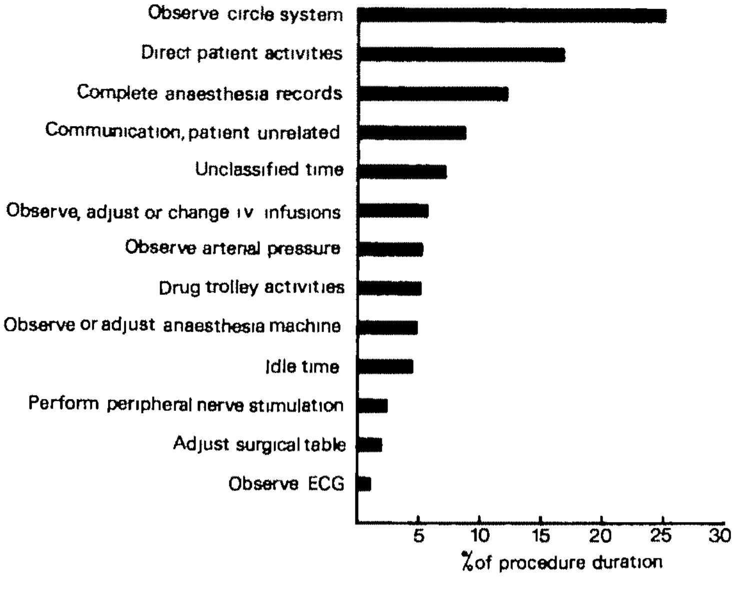

FIG. 1. Results of the activity analysis of intraoperative tasks performed by anaesthetists in 32 surgical procedures.

Remaining activities were classified as either indirect patient or non-patient centered. The number of events ranged from 98 to 930 (mean 349 (SD 394) events). An event was defined as the occurrence of one of 13 activities.

The time and duration of events were recorded and stored digitally on an event recorder (Datamyte 900, Electro General Corp., Minnetonka, MN) by an observer stationed in the operating room. The information gathered by the observer was transferred electronically to a digital computer (HP-9845-A, Hewlett–Packard, Corvallis, OR) for analysis. We performed an activity analysis and a link analysis of the overall intraoperative time duration [4]. In addition, we evaluated how these measurements varied over the duration of the procedure to determine how the anaesthetist allocated time during each 10% time duration segment of the case.

Link analysis is a technique for studying systematically how activities in a process are linked together. The technique is useful for analysing non-standard and non-routine processes in which the activities are not performed in any particular sequence [5]. Link analysis has been used to identify areas of inefficiency in processes that involve humans. Two activities are linked if one activity is followed directly by the other. Links are expressed typically as percentages of the total number of links occurring in a process. Clearly, if a process has m events it has $m-1$ links. In this study there were 78 possible paired activity links. We evaluated the overall frequency of occurrence of each of these links.

RESULTS

Activity analysis

Approximately 17% of the anaesthetist's time was spent in direct contact with the patient. The remaining 83% was spent between indirect patient and non-patient activities (fig. 1). The anaesthetists spent 39% of their time on activities that were unrelated to the immediate care of the patient. The average time spent per event was 0.23 min. On average, more time was spent at each

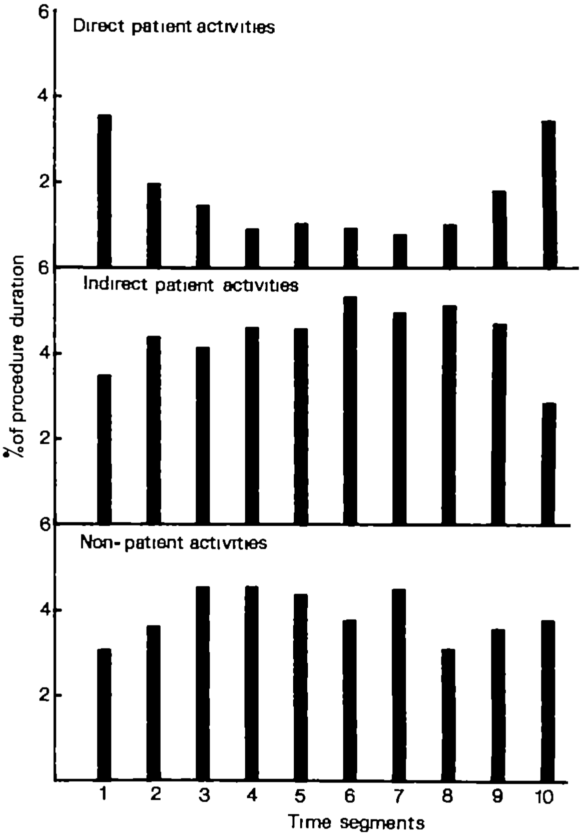

FIG. 2. Distribution of intraoperative activities performed by anaesthetists over 10% time segments of the 32 surgical procedures.

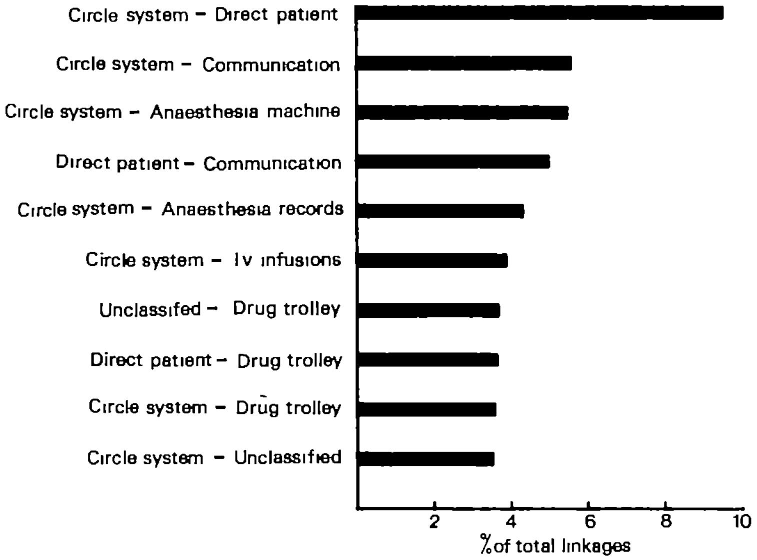

FIG. 3. The 10 most often linked activities. Data are recorded as percentage of the total number of linkages recorded during the 32 surgical procedures.

non-patient event (0.27 min/event) than at each direct (0.24 min/event) or indirect patient events (0.20 min/event).

The time spent at direct patient-centered activities was least in the middle of a procedure (fig. 2).

Link analysis

Of the 78 possible links between any two activities, only one (adjust surgical table – observe ECG) never occurred in any surgical procedure. Forty-eight percent of the 11146 linkages occurring in the 32 procedures involved only 10 pairs of activities (fig. 3). Seven of these pairs had as one of their activities observation of the circle system. Only three pairs included direct patient activity.

DISCUSSION

Kennedy and colleagues [2] noted that the primary intraoperative objectives of the anaesthetist were to observe the patient, observe monitoring equipment and review continuously the management of anaesthesia. In our study, the anaesthetist performed 13 different tasks, only four of which were patient observation activities that made use of training as a specialist physician. In addition, our study also disclosed that the anaesthetist spent only 26 % of the intraoperative time at these activities. This small percentage comprised direct observation of the patient (17 %) and observation of arterial pressure and ECG monitor, and applying the peripheral nerve stimulator (9 %). These values are similar to the findings of Kennedy and colleagues, who reported 16 % of time spent in direct observation of the patient and 11 % in observing monitoring equipment. However, they conflict with the findings of Boquet, Bushman and Davenport [3] who reported that 60 % of the anaesthetist's time was devoted to direct patient management. In our study, the rest of the time was spent in performing tasks arising from observation of the patient (activities 4, 5, 7 and 10) or in performing tasks generally unrelated to immediate patient care (activities 8, 9 and 11–13). In our study, this amounted to 40 % and 34 %, respectively. During this time, the anaesthetist makes less use of acquired medical knowledge and more use of various manual skills.

In our study, direct observation of the patient was clearly at its ebb during the middle 60 % of the surgical procedure (fig. 2). During this time, idle time increased, as did time spent in completing the anaesthesia record. Observation of arterial pressure and applying peripheral nerve stimulation, two of the three indirect information gathering activities, increased only slightly during this period. According to the results of a study on critical incidents [6], anaesthesia mishaps occur most frequently in the middle of the procedure.

Cooper and colleagues [6] also reported that the most frequent mishap involved the breathing system. Unfortunately, they did not report the time distribution of this problem. We have shown that the anaesthetist spends 25 % of his or her time observing the breathing circuit and this activity was concentrated in the last half of the procedure. However, Cooper's study was undertaken at a time when few anaesthetists were using disconnect monitors and when mechanical ventilators were of the type that precluded easy detection of disconnection.

Paget, Lambert and Sridhar [7] suggested that the vigilance of the anaesthetist is adversely affected as the level of complexity in a process (e.g. the delivery of anaesthesia) increases. The level of complexity is determined partly by the number of activities in the process. Ability to spend time on any particular activity will be compromised if there is an increased demand for performance of a large number of tasks during the operation. It seems plausible also that vigilance may be reduced further if the anaesthetist has to perform a series of activities with a different point of focus. An example would be performing a direct patient activity after a non-patient task.

Link analysis has shown that eight activities constituted the 10 most frequently linked pairs of tasks. Only one of these activities (1) involved patient observation; this was linked to activities not having patient observation as a focus. The incidences of linking of two activities involving patient observation (activities 1, 2, 3 or 6) were lower (for 1 and 2, 0.40 %; 1 and 3, 0.25 %; 1 and 6, 0.56 %; 2 and 3, 2.14 %; 2 and 6, 20.4 %; and 3 and 6, 0.73 %).

Several recommendations may be made on the use of operating room personnel and the design of monitoring equipment. To maximize the amount of physician directed patient care, the anaesthetist should spend the majority of his time during the operation observing (directly or indirectly) the patient's physiological status and evaluating the management of anaesthesia. Paraprofessional personnel could be engaged to perform many of the other tasks which are not related to direct patient management. If such individuals had been available to perform activities 4, 5, 7, 8, 9 and 10, the anaesthetists we studied would have had an additional 55% of intraoperative time to observe the patient. The anaesthetist would have needed to expend time on only seven activities, four with the same focus.

Our data suggest that monitoring equipment should be redesigned. The most immediate need is for an automated or semi-automated system for generating the intraoperative anaesthesia record. In our study, 12% of time was spent completing such records manually. Kennedy and colleagues [2] reported that these activities comprised 10–15% of the intraoperative time.

There is also a need for integrated monitoring systems that not only monitor, display and record all important physiological data and drugs administered, but also detect abnormal values and combine data to indicate that adverse events may occur. Such a system would allow the anaesthetist to direct more fully his attention to the immediate care of the patient. It is noteworthy that most of the technology for such a system exists at the present time.

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CARBON DIOXIDE PRODUCTION IN CYANOTIC CHILDREN DURING ANAESTHESIA WITH CONTROLLED VENTILATION†

R. FLETCHER

SUMMARY

Carbon dioxide production and ventilatory efficiency were measured during undisturbed anaesthesia with intermittent positive pressure ventilation in 34 children about to undergo closed or open cardiac surgery. Anaesthesia was provided with fentanyl or halothane and nitrous oxide. There were 15 cyanotic and 19 acyanotic children. Children with cyanotic heart disease produced approximately 20% less carbon dioxide per unit body weight than acyanotic children, but ventilation was approximately 20% less efficient. Adequate ventilation should therefore be obtained when "normal" ventilation in relation to body weight is used in cyanotic children.

The severe hypoxia of cyanotic heart disease depresses oxygen consumption in the awake infant [2] and should therefore depress carbon dioxide production ($\dot{V}CO_2$) also. If these findings apply also to anaesthesia, the reduction in $\dot{V}CO_2$ would be relevant to the choice of ventilator setting for cyanotic infants, as these children also have reduced ventilatory efficiency, that is, increased physiological deadspace.

This paper presents values for $\dot{V}CO_2$ and physiological deadspace (V_D^{phys}/V_T) in a group of cyanotic children about to undergo cardiac surgery. For comparison, a group of patients with acyanotic cardiac disease is also presented. The study was approved by the local Ethics Committee.

PATIENTS AND METHODS

The values for V_D^{phys}/V_T, but not $\dot{V}CO_2$, for some of these children have been published previously [3]. All patients were anaesthetized for open or closed cardiac surgery. Preoperative investigations included cardiac angiography and pressure measurements, echo-cardiography, preoperative arterial blood-gas tensions (Pa_{O_2}) and haemoglobin estimation (Hb).

The acyanotic group consisted of eight children with a normal pulmonary circulation (aortic or pulmonary stenosis), and 11 with left–right (LR) shunts (atrial or ventricular septal defects, or both).

The cyanotic group consisted of four children with transposition of the great arteries, nine with pulmonary stenosis or atresia in combination with a septal defect, one with a common atrioventricular canal and pulmonary hypertension, and one with a double outlet right ventricle syndrome. Large right–left (RL) shunts were demonstrated before operation in all the cyanotic children. No child in either group was in overt left ventricular failure, none had oedema, and none was receiving vasoactive or inotropic drugs other than digitalis or diuretics (table I).

Anaesthesia

Children older than 1 yr were premedicated rectally with a mixture of diazepam, morphine and hyoscine. Anaesthesia was provided with 50% nitrous oxide in oxygen and fentanyl. Two patients in each group also received droperidol. Eleven children (table I) received halothane in place of fentanyl. Ventilation was provided with a Servo ventilator at a rate of 25–35 b.p.m. Constant-flow inspiration was used, with an inspir-

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†Previously presented at the Anaesthetic Research Society [1].

TABLE I. *Patient data (mean (SD); *mean (range))*

	Acyanotic	Cyanotic	P
n	19	15	
Body weight (kg)	11.8 (4.5)	9.1 (3.5)	ns
Body weight/length (kg m^{-1})	13.2 (2.6)	12.1 (2.7)	ns
Age (yr)*	2.7 (0.6–6.8)	1.4 (0.3–4.4)	< 0.05
Haemoglobin (g dl^{-1})	12.8 (0.9)	17.3 (3.6)	< 0.005
Total dose of fentanyl given before measurement ($\mu\text{g kg}^{-1}$)	10.4 (4.8)	11.9 (3.9)	ns
Pa_{O_2} during anaesthesia (kPa)	28.6 (7.2)	7.4 (1.8)	< 0.001
Oesophageal temp. (°C)	36.3 (0.5)	36.2 (0.6)	ns
No. receiving halothane	7	4	ns

atory time of 25% of the cycle, and an end-inspiratory pause of 10%.

Measurements

Carbon dioxide single breath tests (SBT-CO_2) were obtained at steady state after at least 30 min of ventilation. Simultaneously, arterial blood was drawn slowly from a radial or femoral artery cannula, and analysed for Pa_{CO_2}.

The SBT-CO_2 was obtained with a computerized on-line system based on the Servo ventilator and CO_2 Analyzer 930. This system has been described in detail elsewhere [4]. Briefly, the computer takes signals for airway flow, airway pressure and timing from the ventilator, and for airway $P\text{CO}_2$ from the carbon dioxide analyser. The signals, which have been shown to be synchronized [5], are processed to yield the plot of expired $F\text{CO}_2$ against expired volume (SBT-CO_2). The area under this curve is the volume of carbon dioxide in the breath ($V\text{T}_{CO_2}$). From this, $\dot{V}\text{CO}_2$ may be obtained by multiplying by ventilatory frequency.

In order to obtain $V\text{D}^{phys}/V\text{T}$, the computer first calculates the fraction of carbon dioxide in mixed expired gas ($F\bar{E}_{CO_2}$) by dividing $V\text{T}_{CO_2}$ by tidal volume. This value for $F\bar{E}_{CO_2}$ is then substituted in the deadspace equation together with a value for the fraction of carbon dioxide in a gas in equilibrium with arterial blood (Fa_{CO_2}). Fa_{CO_2} is calculated from a supplied value of Pa_{CO_2}, the latter corrected to body temperature by the computer. Body temperature was measured by an oesophageal thermocouple.

Values for $\dot{V}\text{CO}_2$ (and also deadspace) were calculated as the mean of three breaths. The values have been corrected for a tidal volume-dependent error, which arises because small inspiratory tidal volumes do not completely clear the in-line carbon dioxide transducer of expirate. Because the transducer takes a new zero calibration at the end of each inspiration, carbon dioxide molecules remaining in the cuvette at this stage affect measurement of $P\text{CO}_2$ of the subsequent expiration. For instance, $V\text{T}_{CO_2}$ is underestimated by 2.5% at a tidal volume of 100 ml [3].

Statistical analysis was by means of the two-tailed Wilcoxon test (tables I, II), and the two-tailed t test for comparisons of the regressions in figure 1. P values of 0.05 or less were taken to indicate statistical significance.

RESULTS

The mean weights and mean body temperatures of the two groups of children were comparable and the doses of fentanyl were similar (table I). Figure 1 shows the distribution of $\dot{V}\text{CO}_2$ in relation to weight. The regression equations are:

Cyanotic

$$\dot{V}\text{CO}_2\,(\text{ml min}^{-1}) = 24.5 + 4.29 \times \text{weight (kg)}$$
$$r = 0.92, P < 0.001$$

Acyanotic

$$\dot{V}\text{CO}_2\,(\text{ml min}^{-1}) = 35.0 + 5.17 \times \text{weight (kg)}$$
$$r = 0.91, P < 0.001$$

These regressions were significantly different ($P < 0.01$). The slopes of the two regressions were not significantly different, nor were the intercepts at 0 kg; however they differ at 4 kg, which is a

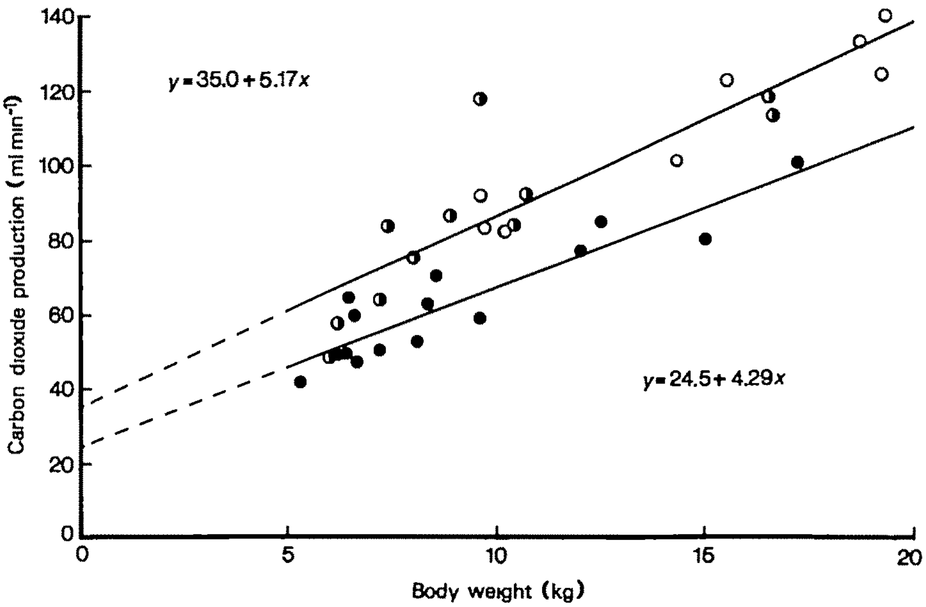

FIG. 1. Carbon dioxide production related to body weight. ● = Cyanotic children; ○ = acyanotic children with normal pulmonary circulation; ◑ = acyanotic children with LR shunts.

TABLE II. *Ventilatory variables (mean values (1SD))*

	Acyanotic	Cyanotic	*P*
$\dot{V}CO_2$ (ml kg^{-1})	8.5 (1.5)	7.3 (1.3)	< 0.01
PE'_{CO_2} (kPa)	4.0 (0.4)	3.9 (0.4)	ns
Pa_{CO_2}(kPa)	4.2 (0.3)	4.9 (0.5)	< 0.001
$\dot{V}E$/weight (ml min^{-1} kg^{-1})	307 (52)	258 (56)	< 0.05
$\dot{V}A$/weight (ml min^{-1} kg^{-1})	219 (33)	152 (29)	< 0.001
VD^{phys}/VT	0.25 (0.05)	0.41 (0.09)	< 0.001
$\dot{V}A/\dot{V}E$	0.75 (0.05)	0.59 (0.09)	< 0.001

more meaningful comparison. If the comparison is restricted to the 23 children who did not receive halothane, the difference in carbon dioxide production remained ($P < 0.02$). Thus a 10-kg cyanotic child has a $\dot{V}CO_2$ of approximately 20% less than that of an acyanotic child of the same weight. Within the cyanotic group there was no relationship between $\dot{V}CO_2$ per unit body weight and physiological deadspace fraction or Pa_{O_2}; that is, the children with the greatest shunts did not necessarily have the lowest metabolic rate.

In order to check if a steady state had been reached at the time of measurement, arterial blood was sampled in 24 children on a second occasion 15–30 min after the first. Group mean Pa_{CO_2} was unchanged in both cyanotic ($P = 0.6$) and acyanotic groups ($P = 1.0$).

The two groups of children received ventilation to virtually the same end-tidal PCO_2 (PE'_{CO_2}), but the acyanotic ones received a greater minute ventilation ($\dot{V}E$) in relation to body weight (table II). The alveolar ventilation ($\dot{V}A$) per unit body weight of the cyanotic children was only 69% of that of the acyanotic children. In addition, the cyanotic children's gas exchange, as measured by VD^{phys}/VT, was less efficient; the ratio $\dot{V}A/\dot{V}E$ (obtained from $(1-VD^{phys}/VT)$), was 0.59, compared with 0.75 in acyanotic children—that is, 20% smaller. Therefore, in spite of the 20% lower $\dot{V}CO_2$ of cyanotic children, their mean

Pa_{CO_2} was significantly greater than that of the acyanotic children (table II).

The mean weight of the 11 acyanotic children with LR shunts was 9.8 kg, compared with 14.6 kg for the eight with normal pulmonary circulation (ns). The latter produced proportionately less carbon dioxide: a mean of 7.8 compared with 9.1 ml kg^{-1} (ns). There was thus no evidence for any difference in $\dot{V}CO_2$ between children with LR shunts (but not in failure) and those with a normal pulmonary circulation (see also figure 1).

DISCUSSION

The use of SBT-CO_2 to measure carbon dioxide elimination has been validated in adults [6] and children [3]. $\dot{V}CO_2$ in the acyanotic children was similar to that observed by Nightingale and Lambert [7].

The results of this study show that carbon dioxide production per unit weight in cyanotic children is 20% less than that of acyanotic children with cardiac disease (in the weight range 5–20 kg).

The ratio of weight to length in the two groups was similar, although the cyanotic children weighed slightly less per metre than the others (table I) and thus their lean body mass per kg should be equal to or greater than that of the acyanotic children. The difference in $\dot{V}CO_2$ cannot be explained, therefore, on the basis of different amounts of metabolically active tissue per kg. It also cannot be attributed to the slightly different proportions of children receiving halothane in the two groups, for the $\dot{V}CO_2$ difference remains if comparison is made between children receiving only fentanyl.

It should be noted that the regression lines in figure 1 do not pass through zero; $\dot{V}CO_2$ does not increase proportionately with weight. It is important, therefore, to specify the weight range if $\dot{V}CO_2$ is expressed per unit body weight. For instance, acyanotic children weighing 15–20 kg have the same $\dot{V}CO_2$ per kg as cyanotic children weighing 5–10 kg (approximately 7.5 ml kg^{-1}), and only 75% of the carbon dioxide production of acyanotic children weighing 5–10 kg. In the present study, comparing group mean $\dot{V}CO_2$ per unit body weight gives a difference between the two groups of 14% — that is, an underestimate. Other authors have observed that cyanotic children have substantially (e.g. 20%) lower mean $\dot{V}CO_2$ values than acyanotic children [8, 9]. However, these differences were found not to be statistically significant, possibly because the results were expressed as $\dot{V}CO_2$ per unit body weight and not as regressions of $\dot{V}CO_2$ against weight.

In the present study, the initial mean Pa_{CO_2} differed between the two groups, but it was unchanged when a second measurement was made 15–30 min later. It cannot be argued, therefore, that the difference in $\dot{V}CO_2$ between groups was the result of carbon dioxide retention by the cyanotic children, hyperventilation in the acyanotic ones, or both; steady state had been achieved at the first measurement.

The mechanism by which hypoxia reduces metabolism in cyanotic children is not clear. Kennaird believes that hypoxia depresses oxygen consumption directly in a thermoneutral environment, and reduces the stress response to cold [2]. Oxygen consumption in children is correlated strongly with caloric intake, and starvation is associated with a significant reduction in $\dot{V}O_2$. However, feeding difficulties are usually not seen in cyanotic children except when there is also cardiac failure, and overt failure was not present in any of the children studied.

Reduced $\dot{V}O_2$ in cyanotic children compared with those with left–right intracardiac shunting has been noted by several authors [10, 11]. Lees and co-workers investigated awake infants and found no differences in $\dot{V}O_2$ between normal and cyanotic children, but $\dot{V}O_2$ in children with LR shunts was significantly greater than in normal individuals [11]. Kennaird [2] also found that infants in whom LR shunting was associated with heart failure consumed more oxygen than normal individuals, and that cyanotic babies consumed much less. Left ventricular failure increases myocardial work and the work of breathing [2].

Thus data from this study and elsewhere suggest that there is a spectrum of metabolic rates in children with cardiac disease. Metabolism, and thus $\dot{V}CO_2$ and $\dot{V}O_2$ per unit weight, are decreased in children with severe hypoxaemia because of RL shunting, and increased in children with LR shunting severe enough to cause heart failure. In the present study, there was no evidence for increased $\dot{V}CO_2$ in children with LR shunts when congestive failure was absent.

The Pa_{CO_2} value is governed by the equation:

$$Pa_{CO_2} = \frac{\dot{V}CO_2}{\text{minute ventilation} \times (1 - V_D^{phys}/V_T) \times \text{constant}}$$

Because both $\dot{V}CO_2$ and the term $(1 - VD^{phys}/VT)$ are reduced by approximately 20% in cyanotic children, it is clear that, had the cyanotic and acyanotic groups received the same ventilation per unit body weight, the group mean Pa_{CO_2} would have been similar. Thus cyanotic children require approximately the same ventilation as normal children during anaesthesia with artificial ventilation in order to achieve normocapnia.

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CARDIAC CONDUCTION INTERACTIONS OF PROPRANOLOL AND VERAPAMIL WITH HALOTHANE IN PENTOBARBITONE-ANAESTHETIZED DOGS

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SUMMARY

We have studied the effects of propranolol 0.25 mg kg^{-1} and verapamil 0.075 mg kg^{-1} on cardiac conduction and refractoriness in 21 dogs anaesthetized with pentobarbitone 30 mg kg^{-1} using His bundle electrocardiography and programmed stimulation. After baseline studies under pentobarbitone and halothane (1.3 MAC) anaesthesia, the dogs were allocated randomly to two groups: group 1 received verapamil followed by propranolol; group 2 received propranolol followed by verapamil; the drugs were given in a continuous infusion over 10 min. The atrial–His (AH) interval, the atrioventricular node effective (AVERP), and functional (AVFRP) refractory periods, were prolonged by verapamil in both groups, but not the His–ventricle (HV) interval or the ventricular effective refractory period (VERP). AVFRP and VERP were prolonged by propranolol in both groups. Corrected sinus node recovery times were normal after each drug. Heart rate and the rate required to produce Wenckebach were decreased by each drug. The combination of verapamil and propranolol during halothane anaesthesia in dogs has significant cardiac conduction effects; however, no spontaneous AV block occurred during the study.

The inhalation anaesthetic agents halothane and enflurane prolong AV nodal conduction [1,2], and in some circumstances (hypertension, hypercapnia and administration of adrenaline, they induce arrhythmias [3,4]. The beta-adrenoceptor antagonist, propranolol, and the calcium entry blocker, verapamil, are used frequently to treat arrhythmias caused by the depressant effect of inhalation anaesthetics on cardiac conduction [5–7]. I.v. propranolol or verapamil, alone or in combination, may be required during inhalation anaesthesia to treat supraventricular arrhythmias in patients with a history of arrhythmias or cardiac disease for which they are receiving calcium or beta-antagonists by mouth. This study has examined the effects of verapamil and propranolol on cardiac conduction and refractoriness in dogs anaesthetized with pentobarbitone and halothane.

MATERIALS AND METHODS

Twenty-one mongrel dogs (13.5–28.5 kg) of both sexes were anaesthetized with pentobarbitone 30 mg kg^{-1} i.v., the trachea was intubated after suxamethonium 80 mg i.m. and the lungs ventilated using a Harvard 607 (TM) ventilator. Anaesthesia was maintained with an i.v. infusion of pentobarbitone 0.5–1.0 mg min^{-1} throughout the experiment. This low-dose continuous infusion is used commonly to provide a stable model in animals for the study of effects of drugs on cardiac electrophysiology [8,9]. The right external jugular vein was cannulated and a 7.5-French gauge pulmonary artery catheter inserted. A catheter was placed in the right femoral artery for measurement of arterial pressure and a 6-French gauge quadripolar His bundle catheter (USCI) in the left femoral artery. The quadripolar catheter was passed retrogradely into the ascending aorta under continuous electrographic monitoring with an ECG–His amplifier on a Gould ES 1000 (TM) monitored recorder until a stable His bundle

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recording was obtained. Standard ECG recordings were obtained with cutaneous electrodes. Through a right thoracotomy, epicardial pacing wires were sutured on the right atrial appendage and anterior–medial surface of the right ventricle. A Medtronics 5325 (TM) programmable stimulator delivering square wave impulses at 1.8 ms duration at twice diastolic threshold was used to pace the heart, and data were recorded on a Gould ES 1000 (TM) eight-channel recorder at a paper speed of 250 mm s^{-1}.

After baseline data were recorded, halothane was administered from a Fluotec Mark III (TM) vaporizer to maintain an end-tidal concentration of 1.13 (0.08)% (1.3 MAC) (as determined by mass spectrometry). Repeat data were recorded. The dogs were subsequently allocated randomly to two groups: group 1 ($n = 10$) received verapamil 0.075 mg kg^{-1} i.v. over 10 min and data were collected, then propranolol 0.25 mg kg^{-1} was given i.v. over 10 min and data were recorded; group 2 ($n = 11$) received propranolol initially, followed by verapamil.

At each data collection, the following variables were measured: the atrial–His (AH) interval (a measurement of atrioventricular node conduction time), the His–ventricle (HV) interval (a measurement of ventricular bundle branch and Purkinje fibre conduction time), the atrioventricular node effective (AVERP) and functional (AVFRP) refractory periods (measurements of AV node repolarization or recovery time), the ventricular effective refractory period (VERP) (a measurement of ventricular recovery time), sinus node recovery times, the heart rate producing Mobitz type I atrioventricular nodal block (Wenckebach) (an indirect measurement of AV node conduction time), and the spontaneous heart rate. The AH interval was measured from the beginning of atrial activity in the intra-aortic electrogram to the beginning of the His potential. The HV interval was measured from the beginning of the His potential to the earliest point of ventricular activity on the electrocardiogram or intra-aortic electrogram. The Q–T interval at constant pacing (pQT) was measured before and after administration of halothane.

The basic cycle length for atrial and ventricular pacing was shorter than the spontaneous cycle length (to achieve stable capture) and was maintained during the study. Determination of refractory period was by using stimuli at increasingly premature intervals until failure of conduction occurred in the tissue studied. As defined by Josephson and Seides [10], the AVERP represents the longest interval between the paced atrial impulse (A_1) and the premature atrial impulse (A_2) that failed to conduct to the His bundle (fig. 1). The AVFRP is the shortest A_1A_2 interval between the paced His impulse (H_1) and the premature His impulse (H_2) that conducted to the ventricle (fig. 1). The VERP corresponds to the longest interval between the paced ventricular impulse and the premature ventricular impulse that failed to capture the ventricle. Sinus node recovery times were measured at paced intervals of 353, 333, 316, and 300 ms. Sinus node recovery times were corrected for heart rate.

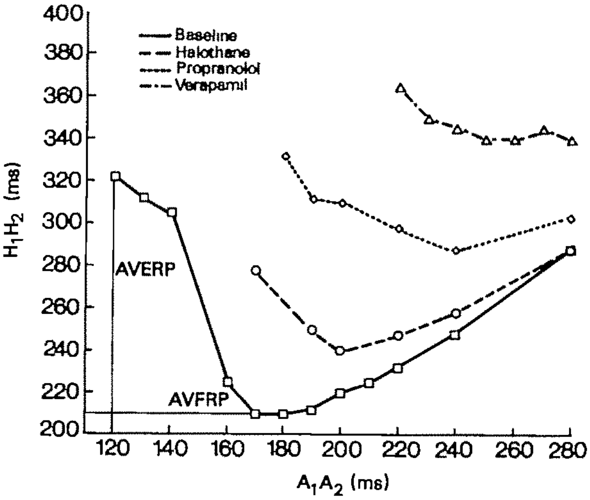

FIG. 1. Illustration of determination of atrioventricular node functional (AVFRP) and effective (AVERP) refractory periods for one dog. A_1A_2 (horizontal axis) is the interval between paced (A_1) and premature (A_2) atrial potentials and H_1H_2 (vertical axis) is the interval from the paced His potential (H_1) to the premature His potential (H_2). AVFRP is the shortest H_1H_2 interval observed or the fastest conduction rate that can be achieved through the AV node. AVERP is the longest A_1A_2 that *fails* to conduct through the AV node to the ventricle. This is measured as 1 ms less than the shortest A_1A_2 interval that conducts to the ventricle. These are indicated at baseline. Note that with each treatment, the curves shift upward and to the right, prolonging both AVFRP and AVERP.

At each data collection, spontaneous heart rate, arterial pressure, cardiac output (in triplicate), central venous pressure, pulmonary artery pressure, pulmonary wedge pressure, serum potassium concentration, temperature, and arterial blood-gas tensions were recorded. Throughout

TABLE I. *Electrophysiological data (mean (SEM)) before and after administration of halothane 1.3 MAC* (n = 21). *AH = atrial–His interval; HV = His–ventricular interval; AVERP = AV nodal effective refractory period; AVFRP = AV nodal functional refractory period; VERP = retrograde ventricular effective refractory period; pQT = QT interval paced at constant rate.* *P < 0.05 *compared with baseline*

Interval	Baseline (ms)	After halothane (ms)	% Change
AH	59 (2.7)	68 (1.9)*	+15
HV	29 (1.0)	29 (1.1)	—
AVERP	125 (10)	151 (8.1)*	+20
AVFRP	200 (7.3)	223 (6.7)*	+12
VERP	141 (2.4)	165 (2.7)*	+17
pQT	380 (10)	410 (10)*	+8

the experiment, systolic arterial pressure was maintained at a value greater than 100 mm Hg with i.v. crystalloid fluid and phenylephrine as required. Ventilation and administration of sodium bicarbonate were adjusted to maintain mean $Pa_{\mathrm{CO_2}}$ at 4.7 (SEM 0.6) kPa and pH at 7.40 (0.1). Supplementary oxygen and positive end-expiratory pressure were used to maintain $Pa_{\mathrm{O_2}}$ greater than 8 kPa. Serum potassium concentration was maintained at 3.5–5.0 mmol litre^{-1}.

Results were analysed using the SAS statistical program and a VAX 730 computer. Measurements of AH, HV, AVERP, AVFRP and VERP were analysed using a Wilcoxon sign rank test. All other data were analysed using parametric *t* tests.

RESULTS

Halothane prolonged significantly AH, AVERP, AVFRP, VERP and the pQT compared with baseline (table I; fig. 1). Halothane did not change the HV interval. The paced rate to induce Wenckebach periodicity varied from 280 (7.6) ms at baseline to 241 (6.3) ms after halothane.

Verapamil prolonged significantly AH, AVERP, and AVFRP when given after either halothane or halothane–propranolol (tables II, III). The paced rate to induce Wenckebach periodicity varied from 231 (7.1) ms after halothane to 199 (6.5) ms after verapamil (group 1) and from 224 (8.6) ms after halothane–propranolol to 194 (11) ms after verapamil (group 2). Verapamil did not effect HV or VERP in either group.

Propranolol significantly prolonged the VERP after either halothane or halothane–verapamil (tables II, III). Propranolol prolonged the HV interval significantly only after halothane in combination with verapamil. It had no significant effect on the AH interval after halothane with verapamil. Propranolol prolonged significantly the AVFRP (both groups) and the AVERP after halothane–verapamil only. The paced rate to induce Wenckebach periodicity varied from 249 (9.7) ms after halothane to 224 (8.6) ms after propranolol (group 2) and from 199 (6.5) ms after halothane–verapamil to 180 (5.2) ms after propranolol (group 1).

AV nodal block did not occur during the study, despite significant effects on AV conduction data. Corrected sinus node recovery times did not change significantly after halothane, verapamil or propranolol.

There were significant reductions in spontaneous heart rate and cardiac output after halothane and after group 1 and group 2 drugs (table IV). After the administration of the second drug (propranolol in group 1; verapamil in group 2), one dog in group 1 and four dogs in group 2 died as a result of severe hypotension and myocardial depression. In all animals, severe hypotension occurred before any electro-

TABLE II. *Cardiac electrophysiological data (mean (SEM)) before and after halothane, verapamil and propranolol (group 1,* n = *10).* *P < 0.05 *compared with preceding value. Abbreviations as in table I*

Interval	Baseline (ms)	After halothane (ms)	After verapamil (ms)	After propranolol (*n* = 9) (ms)
AH	60 (3.3)	72 (4.7)*	102 (12)*	120 (7.0)
HV	30 (1.3)	30 (1.6)	30 (1.7)	33 (1.7)*
AVERP	127 (16)	158 (13)*	206 (17)*	244 (23)*
AVFRP	210 (10)	237 (8.0)*	271 (9.6)*	302 (16)*
VERP	140 (3.5)	164 (4.1)*	170 (4.2)	185 (4.6)*

TABLE III. *Cardiac electrophysiological data (mean (SEM)) before and after halothane, propranolol and verapamil (group 2,* $n = 11$*).* $^*P < 0.05$ *compared with preceding values. Abbreviations as in table I*

Interval	Baseline (ms)	After halothane (ms)	After verapamil (ms)	After propranolol ($n = 7$) (ms)
AH	60 (4.6)	65 (3.6)*	73 (2.4)*	101 (9.6)*
HV	29 (1.5)	28 (1.5)	28 (1.3)	29 (1.5)
AVERP	123 (13)	145 (10)*	159 (13)	229 (23)*
AVFRP	191 (9.9)	211 (9.3)*	236 (8.2)*	290 (15)*
VERP	142 (3.5)	166 (3.7)*	183 (7.7)*	191 (11)

TABLE IV. *Haemodynamic data (mean (SEM)) at baseline and after halothane, group 1 and group 2 drugs. HR = spontaneous heart rate (beat* min^{-1}*); CO = cardiac output (litre* min^{-1}*); MAP = mean arterial pressure (mm Hg); PAWP = pulmonary artery wedge pressure (mm Hg); V = verapamil; P = propranolol.* $^*P < 0.05$ *compared with preceding value*

Measurement	Baseline ($n = 21$)	After halothane ($n = 21$)	Group 1		Group 2	
			V ($n = 10$)	P ($n = 9$)	P ($n = 11$)	V ($n = 7$)
HR	148 (3.5)	126 (2.2)*	112 (3.6)*	104 (5.1)*	115 (2.9)*	107 (5.9)*
CO	3.6 (0.3)	2.9 (0.3)*	2.5 (0.3)*	1.5 (0.1)*	1.8 (0.2)*	1.3 (0.5)*
MAP	138 (10)	106 (6.0)*	102 (1.6)	98 (9)	93 (3.0)*	91 (3.6)
PAWP	12 (1.2)	17 (1.9)*	18 (2.5)	18 (3.8)	18 (3.5)	18 (3.9)

physiological abnormalities, and AV nodal block *per se* was not observed. However, this was not significant between groups (Fisher exact test).

DISCUSSION

Verapamil blocks calcium channels and causes reduced entry of calcium into cardiac cells, which leads to decreased inotropy and chronotropy [11]. Peripheral smooth muscle relaxation produced by verapamil produces reflex increase in sympathetic stimulation which tends to attenuate hypotension partially [11]. Propranolol, a beta-adrenoceptor antagonist, inhibits calcium entry by blocking receptors controlling calcium channels [12]. This results also in negative inotropic and chronotropic responses. Verapamil and propranolol may interact, through different mechanisms inhibiting calcium entry, to produce additive or synergistic adverse haemodynamic or electrophysiological effects. In addition, by reducing the normal reflex sympathetic response to calcium entry blockers, propranolol may produce significant hypotension.

Propranolol decreases hepatic blood flow and reduces clearance of verapamil [13]. As both drugs are metabolized by the liver, competitive metabolic inhibition may reduce elimination, thereby increasing plasma concentrations of both drugs. Verapamil administered to animals receiving propranolol decreased myocardial contractility and prolonged atrioventricular conduction time [14–16]. The combination of infusions of verapamil and propranolol in thiopentone-anaesthetized dogs caused severe haemodynamic alterations and increases in plasma concentrations of both drugs [13]. However, in patients with good left ventricular function who were receiving propranolol by mouth, the addition of i.v. or oral verapamil resulted in some reduction in cardiac output and hypotension which was not clinically significant [17–18]. No significant disturbance occurred in sinus node or AV node conduction. Studying the combination of i.v. verapamil and propranolol in patients with paroxysmal supraventricular tachycardia, Yee, Gulahusein and Klein [19] demonstrated additive effects on AVFRP and noted no significant hypotensive problems or AV nodal block.

Halothane also has calcium entry blocking effects which produce negative inotropy and chronotropy [20]. Halothane prolongs AV nodal conduction time and prolongs HV conduction time [1,21–23]. Administration of combinations of verapamil and propranolol during halothane anaesthesia may cause additive or synergistic effects as all three drugs influence calcium conductance. Inhalation anaesthetics increase plasma concentrations of verapamil by decreasing the steady state volume of distribution and reducing total clearance [24]. Significant depression of contractility occurs after verapamil in dogs during anaesthesia with halothane and enflurane, but is absent during isoflurane anaesthesia [25]. Halothane also reduces liver blood flow, decreases the metabolism of propranolol and increases plasma concentrations of propranolol in dogs [26]. Kapur and Flacke [24] studied the effects of i.v. verapamil 0.2 mg kg^{-1} during 1.1 MAC halothane anaesthesia in dogs anaesthetized initially with thiopentone. Significant reductions in mean arterial pressure and left ventricular contractility occurred with prolongation of the PR interval and episodes of second degree and third degree heart block.

The doses of propranolol (0.25 mg kg^{-1}) and verapamil (0.075 mg kg^{-1}) we have used were shown in previous canine studies to achieve adequate plasma concentrations and significant electrophysiological changes [27–28]. Although we have not measured plasma concentrations, our results suggest that significant concentrations of each drug were reached, and our data were obtained immediately after discontinuing the infusions of verapamil and propranolol.

Our study has demonstrated that halothane prolonged significantly AV node conduction time and refractoriness, in addition to ventricular refractoriness. Our observations that halothane has no effect on HV conduction time differ from those of others [1,21], although Morrow, Logic and Haley [29] noted no change in HV intervals during halothane administration under pentobarbitone anaesthesia. Verapamil maintained electrophysiological and haemodynamic effects after halothane and halothane–propranolol. These effects appeared to be additive; however, the death of four dogs in group 2, compared with one death in group 1, suggests a more significant haemodynamic interaction when verapamil is administered after propranolol during halothane anaesthesia. This could result from a greater reduction in calcium entry or an increase in plasma concentrations of verapamil or propranolol, or both, because of metabolic inhibition by competition between the drugs or by halothane. However, we cannot exclude an effect of pentobarbitone, which could contribute especially to the severe haemodynamic depression. Although propranolol alone depresses only AV conduction and refractoriness [5], it had significant effects on VERP after halothane and halothane–verapamil in the present study. In addition, the AH interval was not changed significantly when propranolol was administered after halothane–verapamil, demonstrating attenuation by prior administration of verapamil. Pentobarbitone may have attenuated AV node depression by increasing sympathetic tone, especially after the initial bolus. However, the low doses of the continuous infusion during which our data were collected should have limited this effect.

In summary, we have demonstrated that halothane significantly prolonged AV nodal conduction time, AV nodal refractoriness, ventricular refractoriness and the paced QT interval. AV nodal depression produced by verapamil was additive to that from halothane and halothane–propranolol. The effects of propranolol were additive also, but varied, with unexpected significant prolongation of the VERP occurring after halothane and halothane–verapamil. The administration of i.v. verapamil and propranolol in any order during halothane anaesthesia has profound additive effects on cardiac electrophysiology.

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DEVELOPMENTAL NEUROPHYSIOLOGY OF MAMMALIAN PERIPHERAL NERVES AND AGE-RELATED DIFFERENTIAL SENSITIVITY TO LOCAL ANAESTHETIC

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SUMMARY

Using an in vitro *nerve preparation, we have studied the relative electrophysiological properties of myelinated and unmyelinated nerve fibres in the vagus nerve of 1-, 9- and 36-month-old rabbits and their sensitivity to local anaesthetic. The baseline (values before infusion of local anaesthetic) mean amplitude and conduction velocity (CV) of the compound action potential (APc) were recorded and the nerve was exposed to a range of concentrations (0.5–4.0 mmol litre*$^{-1}$*) of lignocaine for periods sufficient to attain equilibrium block. There was an increase in the amplitude of the A fibre elevation from the 1-month to the 9- and 36-month-old rabbits. The CV of the A and B fibres increased significantly with age, while the CV of the C fibres did not change. The* ED_{50} *values of lignocaine for reduction of the A fibre elevation in the 1-, 9- and 36-month-old rabbits were 0.66, 0.94 and 0.85 mmol litre*$^{-1}$*, respectively. The respective values for the B fibres were 0.74, 1.21 and 0.82 mmol litre*$^{-1}$*, while those of the C fibres were 1.50, 2.44 and 2.07 mmol litre*$^{-1}$*. In general, nerves from young and old rabbits were more sensitive to local anaesthetic-induced conduction blockade, suggesting that smaller doses of local anaesthetic are required clinically for anaesthesia in paediatric and older age groups.*

The use of regional anaesthesia has increased recently in paediatric practice [1–6]. Caudal anaesthesia has been used in newborn subjects [4,5,7], while spinal anaesthesia has been used in premature infants [1,2]. The dose and concentration of the local anaesthetic has been based on either the child's weight [3,4,7] or its age [8,9]. None of these studies compared the characteristics (onset, quality and duration) of nerve blockade in this age group with that of an adult. The effect of increased age on dose requirements for extradural [10,11] and spinal [12–14] anaesthesia is not clear, and there is a need to compare the sensitivities to local anaesthetic, of the nerves of different age groups.

This study has investigated the effect of age on local anaesthetic sensitivity using an *in vitro* mammalian nerve preparation. Utilizing the comparative biological data of man and experimental animals [15,16], nerves from rabbits of varying ages were studied which were comparable to young, adolescent and adult age groups. We also examined the relative electrophysiological properties of myelinated and unmyelinated fibres in the rabbit vagus nerve by comparing the conduction velocities (CV) and amplitudes of the compound action potential (APc) of the A, B and C fibres in the three age groups.

MATERIALS AND METHODS

We studied New Zealand White rabbits of 1, 9 and 36 months of age. Puberty in man (13.5 (2.5) yr) is equivalent to 7.0 (1.5) months in rabbits [16]. The 9-month old rabbit was chosen

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as representative of a 15–20-yr-old person. The 4-week old, recently weaned rabbits were considered to be the equivalent of a 1–3-yr-old child. The average life span in man is 73 yr [16], while that reported for rabbits varies greatly, from 2 [15] to 13 [16] yr. The 36-month-old retired breeders, the oldest obtainable from the breeding laboratories, were considered to represent adult human beings.

The rabbits were housed in the Harvard Medical School, NIH approved, animal care facility in accordance with the *Guide for the Care and Use of Laboratory Animals* (DHHS publication No. (NIH) 78–23, revised 1978). Animals were also treated in accordance with the Harvard Medical School *Guidelines for Animal Care and Use of Laboratory Animals*. The 9- and 36-month-old rabbits were anaesthetized with thiamylal 30–40 mg i.v., while the 1-month old rabbits were anaesthetized with pentobarbitone 50 mg i.p. They were then killed by air embolism and the vagus nerves removed within 10–15 min. The excised nerves were stored in Liley solution, at room temperature (20–22 °C) and aerated with 100% oxygen. The Liley solution consisted of (mmol litre^{-1}): NaCl 136.8; KCl 5.0; $CaCl_2$ 2.0; $MgCl_2$ 1.0; dextrose 11.0; Hepes buffer [4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid] 2.53. The pH of the solution was adjusted to 7.4 (0.02) by the addition of sodium hydroxide 1 mol litre^{-1} [17].

The nerves were cleaned of adventitious tissue by microdissection, and mounted on a nerve chamber with the sheath intact. The design of the nerve chamber, the procedure for nerve stimulation and recording of the APc have been described previously [17]. In brief, the nerve was stimulated at one end by passing current between two platinum electrodes in contact with the nerve at points separated by 2.5 mm in a zone isolated from the test pool, which contained the control or anaesthetic-containing solution. This pool extended over a 5-cm length of nerve and contained the two recording electrodes, also of platinum wire, and spaced at 4.0 and 4.7 cm from the nearer stimulating electrode. The stimulus was a square wave supplied by a Grass S48 stimulator (Grass Instrument Co., Quincy Ma), of duration 0.05 ms for A fibres, 0.1 ms for B fibres and 1.0 ms for C fibres, and of a strength 1.5–2 times that required to elicit a compound action potential of greatest amplitude for the respective fibre types.

The externally recorded, differential, biphasic compound action potentials were amplified ×50 (Model A47 uu Differential Electrometer, Metametrics, Inc., Cambridge, Ma) and recorded on a storage oscilloscope (Tektronix, Portland, Or). The peak amplitude of the component of each biphasic elevation of the APc, and its latency, were used as a measure of the CAP magnitude and conduction velocity for each respective fibre type. Conduction velocity was calculated by dividing the conduction distance (40 mm) by the latency (in ms) to yield the group velocity in m s^{-1}. Stimuli for each fibre type were delivered at 5-min intervals. The fibres were identified by their conduction velocity: A fibres conduct impulses at 20–50 m s^{-1}, B fibres at 5–15 m s^{-1} and C fibres at less than 2 m s^{-1}.

The effect of 12 different concentrations of lignocaine (0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5 and 4.0 mmol litre^{-1}) was investigated on the elevations of APc from A, B and C nerve fibres of the vagus nerve of each of the different age groups of rabbits. The sequence of lignocaine concentration tested was randomized using a random number generator. Fresh Liley and lignocaine solutions were prepared each day.

In each experiment, a baseline period of 30 min assured stability of the APc, during which time the Liley solution perfused the nerve at 0.5 ml min^{-1}. Following this, a solution of lignocaine in Liley perfused the nerve at 0.5 ml min^{-1} for at least 30 min or until equilibrium block occurred. Equilibrium block was considered to have been attained when the change in the amplitude of the APc was 5% or less for 10 min. Only one nerve was tested at each lignocaine concentration. After equilibrium block, the nerve was washed with the Liley solution until 80% of the baseline amplitude of the APc was restored.

Differences in the baseline mean amplitudes and mean CV of the APc of the A, B and C fibres (values after 30 min of measurement in Liley's, before lignocaine infusion) between the three age groups were compared by analysis of variance and Bonferroni correction of the unpaired Student's *t* test [18]. To determine the relative changes between the A and C fibres, the ratio of the amplitude of the A to the C fibre elevation in the three age groups was obtained.

The percent decrease of the APc amplitude from control values during equilibrium block was determined after each experiment. Dose–response curves for each nerve fibre type were generated after log–probit transformation, using those data pairs with which there was less than 100% blockade. This transformation converts a sigmoid curve to linearity in the 1–99% response range. The method of least squares analysis was used to plot linear regression lines and to derive the ED_{50}, the point of 50% depression of the APc amplitude. Differences between the responses of the A, B and C fibre elevations across the three age groups were determined by analysis of covariance [19].

RESULTS

The mean amplitude of the A fibre elevation of the 1-month-old rabbits was significantly ($P < 0.05$) smaller (47–53%) than those of the other groups. The mean amplitude of the C fibre elevation in the 1-month-old rabbits was significantly ($P < 0.05$) greater (43%) than that in the 9-month-olds, but not different from that in the adult rabbits (table I). There was no significant difference in the mean amplitude of the B fibre elevations between the three age groups or of the A and C fibre elevations between the adolescent and adult rabbits. The increase in the amplitude of the A fibres, coupled with the decreased amplitude of the C fibre elevations produced an increased A:C ratio (270%) as the rabbits reached adulthood (table I).

The CV of the A and B fibres in the 1-month-old rabbits were significantly ($P < 0.05$) slower (58–62%) than those of the other two age groups. There was no significant difference in the CV of the C fibres between the three age groups or in the CV of the A and B fibres between the adolescent and adult rabbits (table II).

The compound action potentials of the A fibres in the 1-month-old rabbits were blocked completely by lignocaine concentrations of 2 mmol litre^{-1} or greater, those of the 9-month-old rabbits by lignocaine 2.5 mmol litre^{-1} or more, and those of the 36-month-olds, by 2.25-mmol litre^{-1} or greater concentrations (table III). The slopes (means (SD)) of the log–probit linear regressions for the A fibres (fig. 1) for the 1-, 9- and 36-month-old rabbits were 2.5 (0.33), 2.06 (0.32) and 1.81 (0.38) (correlation coefficients were 0.96, 0.94 and 0.91), respectively. The ED_{50} values of lignocaine for A fibres in the 1-, 9- and 36-month-old rabbits were 0.66, 0.94 and 0.85 mmol litre^{-1}, respectively. The A fibre elevations of the 1-month-old rabbits were more sensitive to lignocaine than those of the 9-month-old ($P < 0.05$) and the 36-month-old animals ($P < 0.05$). The responses of the A fibres of the 9- and 36-month-old rabbits were not significantly different ($P > 0.05$).

TABLE I. *Mean (SD) amplitudes (mV) of action potentials of A, B and C nerve fibres in three age groups of rabbits. Significant differences ($P < 0.05$): *smaller than other two groups; †larger than in 9-month-old*

Nerve fibre	Age (months) 1 ($n = 12$)		9 ($n = 12$)		36 ($n = 12$)	
A	1.24	(0.4)*	2.34	(0.6)	2.66	(0.8)
B	0.98	(0.5)	0.84	(0.4)	0.78	(0.4)
C	0.6	(0.2)†	0.42	(0.1)	0.48	(0.1)
A:C ratio	2.2	(0.7)	5.9	(2.1)	5.7	(1.8)

TABLE II. *Mean (SD) conduction velocities ($m\ s^{-1}$) of the A, B and C nerve fibres in three age groups of rabbits. * Significantly slower than other two groups ($P < 0.05$)*

Nerve fibre	Age (months) 1 ($n = 12$)		9 ($n = 12$)		36 ($n = 12$)	
A	26	(4)*	40	(4)	38	(4)
B	7	(1)*	12	(2)	12	(2)
C	1.1	(0.1)	1.2	(0.1)	1.2	(0.1)

TABLE III. *Percent blockade of the A fibre compound action potential in three age groups of rabbits*

Lignocaine concn (mmol litre^{-1})	1 Month	9 Months	36 Months
0.5	38	22	31
0.75	46	14	38
1.0	73	60	38
1.25	96	50	57
1.5	96	85	89
1.75	99	94	93
2.0	100	95	97
2.25	100	97	100
2.5	100	100	98
3.0	100	100	100
3.5	100	100	100
4.0	100	100	100

There was an increased block of the nerve action potential of the B fibres with higher concentrations of lignocaine, except in the 1-month-old rabbits, in which one nerve exhibited extreme sensitivity (100% block after 20 min exposure) to lignocaine 1.25 mmol litre^{-1}; it recovered to 100% of its baseline APc value after washout of lignocaine (table IV). The B fibre action potentials were abolished completely in the

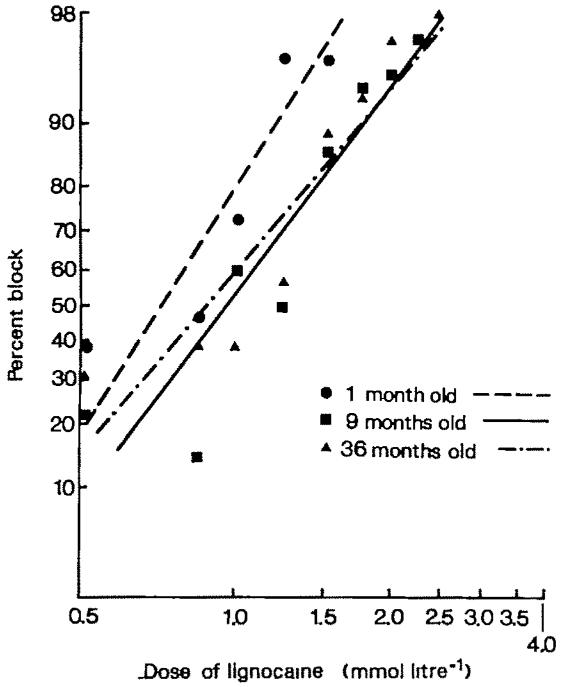

FIG. 1. A Fibres. Log dose–probit response relationships for lignocaine in the 1-month, 9-month and 36-month-old rabbits, with regression lines.

TABLE IV. *Percent blockade of the B fibre compound action potential in three age groups of rabbits*

Lignocaine concn (mmol litre^{-1})	1 Month	9 Months	36 Months
0.5	32	16	29
0.75	33	14	44
1.0	52	47	52
1.25	100	41	65
1.5	78	54	82
1.75	67	59	93
2.0	95	69	91
2.25	88	76	96
2.5	100	98	100
3.0	100	94	100
3.5	100	100	100
4.0	100	100	100

1- and 36-month-old rabbits by lignocaine concentrations of 2.5 mmol litre^{-1} or more; that of the 9-month-old, by 3.5 mmol litre^{-1} or more. The slopes (mean (SD)) of the B fibre linear regression (fig. 2) for the 1-, 9- and 36-month-old rabbits were 1.31 (0.58), 1.63 (0.37) and 1.58 (0.17) (correlation coefficients 0.68, 0.86 and 0.97),

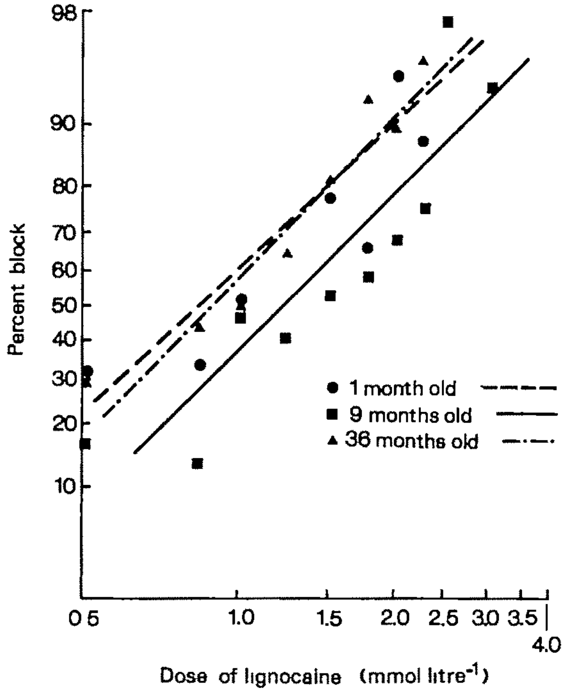

FIG. 2. B Fibres. Log dose–probit response relationships for lignocaine in the 1-month, 9-month and 36-month-old rabbits, with regression lines.

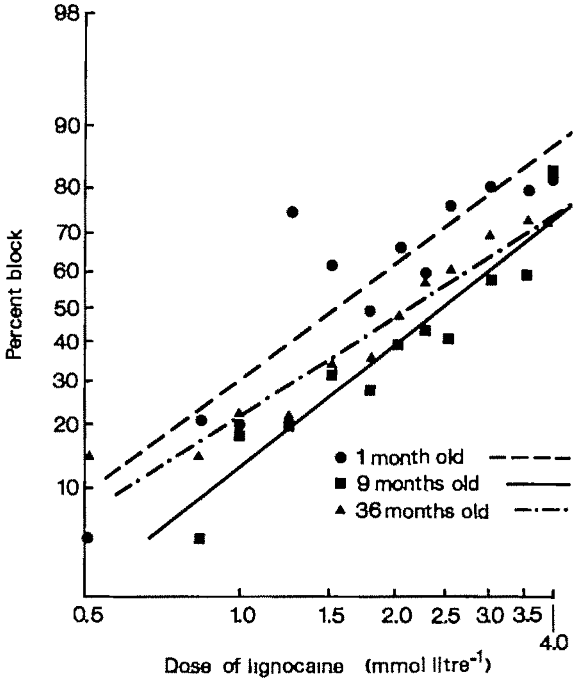

FIG. 3. C Fibres. Log dose–probit response relationships for lignocaine in the 1-month, 9-month and 36-month-old rabbits, with regression lines.

TABLE V. *Percent blockade of the C fibre compound action potential in three age groups of rabbits*

Lignocaine concn (mmol litre^{-1})	1 Month	9 Months	36 Months
0.5	5	0	14
0.75	21	5	14
1.0	20	18	23
1.25	75	20	20
1.5	62	33	35
1.75	49	28	36
2.0	67	40	48
2.25	60	44	58
2.5	77	42	61
3.0	81	59	70
3.5	80	60	73
4.0	82	84	72

respectively. The ED_{50} values of lignocaine for the B fibre elevations in the 1-, 9- and 36-month-old rabbits were 0.74, 1.21 and 0.82 mmol litre^{-1}, respectively. The B fibres of the 36-month-old rabbits were significantly ($P < 0.05$) more sensitive to lignocaine than those of the 9-month-old rabbits. The B fibre responses between the 1- and 9-month-old and the 1- and 36-month-old rabbits were not statistically different ($P > 0.05$).

Greater degrees of blockade of the C fibres were noted in the 1- and 36-month-old rabbits (table V). The slopes (mean (SD)) of the linear regression for the C fibres (fig. 3) in the 1-, 9- and 36-month-old rabbits were 1.18 (0.18), 1.28 (0.12) and 0.98 (0.08) (correlation coefficients 0.91, 0.96 and 0.96), respectively. The ED_{50} values of lignocaine for the C fibres in the 1-, 9- and 36-month-old rabbits were 1.50, 2.44 and 2.07 mmol litre^{-1}, respectively. The dose–response relationships for the C fibre elevations from the three age groups were found to be significantly different ($P < 0.05$) from each other (1 *v.* 9 months; 1 *v.* 36 months and 36 *v.* 9 months).

DISCUSSION

The compound action potential is a complex electrical signal comprising the sum of potential changes between the recording electrodes resulting from electrical current flow. Each fibre in the nerve generates an extracellular current depending both on its passive electrical properties (membrane and axoplasmic resistance, and membrane capacitance) and on the density of ionic channels and thus of active currents. The portion of this current that flows between the two recording electrodes is dependent further on the resistive and capacitative properties of the whole nerve, the position of the particular fibre within the bundle, and the position and electrical characteristics of insulating adventitia, such as the perineurium. Furthermore, fibres of different conduction velocities deliver action current to the recording electrodes at different times, the compound action potential summing these signals to yield a net potential from all individual fibre currents dispersed by their various arrival times and durations.

As we used 1.5–2 times supramaximal stimuli, we assume that we excited all the fibres. Although we do not know the intrinsic passive electrical properties of the vagus nerves from the animals of different ages, their overall diameter was approximately the same and the interstitial space in fixed tissue, judged by examining the histological data from de Neef, Jansen and Versprille [20], was equally comparable. Therefore, we assume that the amplitude of the APc increases with the number of fibres conducting, although possibly in a disproportionate manner, as neither the extent of dispersion nor the action current per fibre is known.

We found an increase in the amplitude of APc elevations of myelinated relative to non-myelinated fibres with age (table I). The greater amplitude of the A fibre elevation in the 9- and 36-month-old rabbits may result from a greater number of myelinated fibres in these age groups. In a study of the developmental morphology of the rabbit vagus nerve, de Neef, Jansen and Versprille [20] found that the relative number of myelinated fibres increased from 2% at birth to 6% at 15 days and 9% in adult rabbits. Alternatively, the APc elevations could also increase because of an age-related reduction in the degree of dispersion; the conduction velocities in myelinated fibres of 9-month-old rabbits may have been more uniform than those in 1-month-old animals if, for example, the density of sodium channels or the extent of myelination varied more in the younger animals.

A decrease in the amplitude of the compound action potential with advancing age has been observed in man [21–23]. This is probably related to a decrease in the number of nerve fibres with ageing [20–24]. However, in the present study the amplitude of the A, B and C fibres in the 9- and 36-month-old rabbits were not statistically different (table I). Our results agree with those found in other experimental animals. Birren and Wall [25] found no change in the refractory period (size and duration of the action potential) of the sciatic nerve between the 300-day-old and 850-day-old rats. In a review of the pathophysiology of neuronal ageing, Ritchie [24] noted differences in the results between human and animal studies. Change in compound action potential amplitude with ageing is less in experimental animals compared with man. Results reported for man, however, are not unequivocal. Lehman, Muche and Schutt [21] observed that there was no significant relationship between the refractory period (latency and amplitude of the test response) of the sural nerve action potential and advancing age up to 70 yr.

The increases in the conduction velocities of the A and B fibres from the 1-month to the 9-month rabbits (table II) are consistent with the findings of de Neef, Jansen and Versprille [20]. The increase in the conduction velocity is thought to be related to an increase in nerve fibre diameter—that is, extent of myelination [20,26]. In our study, the CV of the C fibres in the three age groups were found to be the same. Unmyelinated nerve fibres achieve their maximum conduction velocities at an earlier age; the CV of the unmyelinated nerve fibres were found to be the same in the 15-day-old compared with the adult rabbit [20].

The changes in CV seen with ageing are different in humans compared with experimental animals [24]. In man, there is a reduction of CV with increased age [23,27–29]. The magnitude of the change, however, is small [24]. The slowing in conduction velocity with age is probably a result of selective disappearance of the larger diameter fibres [30,31]. This may also result from a decrease in internodal length, with an increased number of potassium channels appearing at newly formed nodes after spontaneously occuring demyelination followed by remyelination [24]. This decrease in CV was not seen in rats: CV values for the 350-day and 650-day-old rats were 59 m s^{-1} and 60 m s^{-1}, respectively [25]. The CV in the rat nerve apparently increases as the animal reaches maturity, after which it remains the same [24]. Our study showed this occurred with the B and C fibres of rabbits. The insignificant slowing of CV of A fibres in the 36-month-old rabbits may reflect an initial diminution of the larger diameter fibres with increased age [30,31].

We observed that, in general, the APc was more sensitive to lignocaine in the nerves from the youngest animals than in those from the older ones. The reduction in APc produced by drugs may be caused by at least two factors: extinction of impulses in some individual fibres and differential slowing of conduction in others, resulting in greater dispersion. We noted that the relative increase in latency with equal doses of lignocaine was the same among nerves from animals of all three ages and thus we conclude that whatever further dispersion resulted during lignocaine block was not the cause of the greater sensitivity of the youngest nerves.

The A fibres of the 1-month-old rabbits were more sensitive to lignocaine than those of the two older age groups. This may result from incomplete axonal growth with less myelination in the young rabbits. Our findings confirm an earlier study of *in vitro* compound action potential on desheathed dog sciatic nerves: the ED_{50} of lignocaine for the A fibres was 120 µmol $litre^{-1}$ for the neonatal (24–96-h-old dogs) nerves and 280 µmol $litre^{-1}$ for the adult nerves [32]. Although the degree of blockade of the B fibres of the 1-month-old rabbits was greater than in the 9-month-olds, the difference did not reach statistical significance ($P = 0.106$).

Experience with spinal anaesthesia in premature and high risk infants showed remarkable cardiovascular stability: no episode of hypotension or bradycardia was noted [1,2]. The same stability was found after caudal anaesthesia in children, despite high levels of blockade [4]. McGoon stated that arterial pressure was more stable in younger children [4]. The C fibres of the 1-month-old rabbits were found to be more sensitive to lignocaine. Penile nerve block in children for circumcision and hypospadias repair has provided pain relief for as long as 24–48 h [3,6].

The B and C fibres in the 36-month rabbits were more sensitive to lignocaine than those in the 9-month-old. In older patients, faster onset and higher levels of nerve blockade have been observed after spinal and extradural anaesthesia [10,12,14], resulting in an increased frequency and a greater degree of hypotension [14]. This greater sensitivity may reflect diminution in the number and diameter of the nerve fibres from vascular insufficiency, repeated trauma, toxic effects of compounds and diseases common in the adult [24].

In clinical practice, factors other than increased intrinsic sensitivity of the nerve may play a role. Differences in the level, intensity and duration of nerve blockade may also result from differences in vascular supply, capacity of the extradural space, patency of the intervertebral foramina, inflammation of or fibrosis within the nerve roots, and the amount of extradural fat and venous and lymphatic plexuses [10,11,33,34].

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PARKINSONISM AND THE ANAESTHETIST

A. M. SEVERN

This review considers the relevance of Parkinsonism to the anaesthetist. The subject was reviewed last in 1977 [9]. Parkinsonism is of interest to anaesthetists for two reasons: first, anaesthetists are requested increasingly to manage elderly patients, a group in whom Parkinson's disease is relatively common; second, certain features of Parkinsonism are similar to acute disturbances of motor control during or after anaesthesia: common mechanisms may be involved. A distinction can be made between idiopathic Parkinson's disease and other forms of Parkinsonism, although the clinical syndrome is similar. The cardinal features of Parkinsonism are hypokinesia, rigidity and tremor [51, 70]. Idiopathic Parkinson's disease is the form of Parkinsonism most likely to be encountered by the anaesthetist. It is an important cause of morbidity in the elderly and estimates of prevalence vary between 59 and 187 per 100000 population [35].

PARKINSONISM: A DESCRIPTION

Clinical features

Hypokinesia is characterized by difficulty in initiating and slowness in executing movement. Phonation and swallowing may be affected. Chest wall movement is reduced and restrictive ventilatory defect may occur. Rigidity differs from that of corticospinal tract lesions, being present characteristically throughout the whole range of movement of a joint with a "lead-pipe" or "cogwheel" quality. Tremor is most pronounced at rest and has a frequency of 4–8 Hz. It may be absent in some patients. Other features of Parkinsonism include autonomic dysfunction, with salivation, postural hypotension and disorders of respiratory control. Mood changes may reflect the patient's despair or may be part of a global deterioration of central nervous system function. Similarities between Parkinsonism and Alzheimer-type dementia have been described.

Aetiology

Specific agents have been blamed for certain types of Parkinsonism. A pandemic of encephalitis lethargica between the two World Wars was responsible for Parkinsonism with early onset, severe rigidity and disordered respiratory control. Post-encephalitic Parkinsonism is very rare today, since there are few survivors of the pandemic. Heavy metal and carbon monoxide poisoning cause Parkinsonism. Drug-induced Parkinsonism results from dopamine receptor blockade by neuroleptic drugs.

Parkinsonism was observed recently in American drug addicts using an illicitly manufactured pethidine analogue [46]. A neurotoxin, 1-methyl-4-phenyl-1,2,5,6,tetrahydropyridine (MPTP) was found as a contaminant of this drug and shown subsequently to produce Parkinsonism in primates.

The MPTP-treated primate is a useful animal model for the study of Parkinsonism. It has been shown that the neurotoxicity of MPTP depends on the activity of brain monoamine oxidase (Type B enzyme) and that prophylaxis against its effects in animals is possible by using selective monoamine oxidase inhibitors [33, 47]. It is interesting that the lower incidence of Parkinson's disease in smokers has been attributed to inhibition of monoamine oxidase Type B by products of tobacco combustion [76]. These observations have prompted a search for possible neurotoxins in the environment—toxins which are chemically similar to MPTP or which depend on activation by monoamine oxidase. Despite this interest, the aetiology of Parkinson's disease remains unknown.

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Pathophysiology

Parkinsonism is a disorder of the dopamine pathways of the basal ganglia. Dopaminergic pathways project from the substantia nigra to the striatum. Histological sections of this region in Parkinsonism show a loss of the pigment of the substantia nigra. The pigment is a marker of catecholamine metabolism.

Approximately 80% of the dopamine content of the striatum is lost before Parkinsonism is apparent clinically. When degeneration is less advanced, there is some compensation in surviving neurones. Dopamine production is increased in surviving neurones and there is a proliferation of dopamine receptors on the post-synaptic sites of the striatum. These observations lend support to the theory that there may be a long period of "subclinical" Parkinsonism in the natural history of Parkinson's disease, a theory that has important implications to those concerned with epidemiology and prophylaxis.

The basal ganglia influence movement through efferent pathways to the cortex. The nature of that influence depends upon the balance of cholinergic and dopaminergic activity within the basal ganglia. The two systems may be regarded usefully as having mutually antagonistic actions.

Treatment

Treatment is aimed at restoring the activity of dopamine in the striatum. Dopamine does not cross the blood–brain barrier, so its immediate precursor, levodopa (L-Dopa) is used. This is decarboxylated within the brain to produce the active neurotransmitter. This approach has disadvantages as decarboxylation of L-Dopa to dopamine outside the central nervous system results in unacceptable degrees of cardiovascular instability, and the need for large doses of L-Dopa at frequent intervals [15]. The use of benserazide or carbidopa to prevent the peripheral breakdown of L-Dopa was a significant breakthrough in treatment and allowed a substantial reduction in dose. These decarboxylase inhibitors are formulated with an appropriate dose of L-Dopa and are marketed under the brand names Madopar and Sinemet.

Although anticholinergic agents have been supplanted largely by L-Dopa, there remain specific indications for their use. They are useful where rigidity is the major symptom. Anticholinergic drugs used in Parkinsonism include benztropine, benzhexol and orphenadrine.

Other approaches to treatment involve making dopamine more available at the postsynaptic receptor of the striatum. Such methods include stimulation of dopamine release by amphetamine, blocking pre-synaptic uptake of dopamine with amantadine or inhibition of metabolism with monoamine oxidase (type B) inhibition. A novel approach to treatment is the method of implanting a graft of fetal brain tissue or the patient's adrenal tissue into the patient's brain. This method has received a considerable amount of media attention in the past few months, in the U.K., but has not been evaluated in the long term. Surgical treatment, using stereotactic techniques to produce isolated brain lesions is currently the subject of some hopeful research.

Monoamine oxidase inhibition has an important role, both historically and in contemporary practice, in the treatment of Parkinsonism. Non-selective inhibition of monoamine oxidase is no longer used because severe cardiovascular side effects result from an interaction between L-Dopa and monoamine oxidase inhibition. Selective inhibition of the type B enzyme, found in the central nervous system, prevents the breakdown of brain dopamine without affecting the metabolism of noradrenaline in peripheral nerve endings. The combination of the type B inhibitor selegiline and L-Dopa is safe [5] and the use of selegiline before anaesthesia would not be expected to be associated with the problems associated with non-specific enzyme inhibition; certainly, there have been no reports of adverse cardiovascular side effects [K. Davies, Britannia Pharmaceuticals, personal communication].

The observations that monoamine oxidase inhibition protects against environmentally induced Parkinsonism and that the disease may exist in a subclinical form offer new perspectives on treatment. If a population with a high risk of developing Parkinsonism could be identified, prophylaxis with monoamine oxidase inhibition would be worthwhile. The new imaging technique, positron emission tomography (PET), can detect subtle changes in metabolism in the basal ganglia [31, 48]. It may have a role in detecting subclinical Parkinsonism.

Complications of treatment

Neurological side effects result from excessive stimulation of the striatum by dopamine and include dyskinesia, nausea, psychoses and nightmares. A difficult aspect of L-Dopa treatment is the development of resistance to the drug with a requirement for larger doses, and a greater risk of side effects. This is partly because the replacement of brain dopamine does not halt the progression of nigral neurone degeneration. After chronic treatment, a particularly difficult and distressing complication is the "on-off" syndrome, in which the patient alternates between periods of inactivity with rigidity and activity. Infusions of L-Dopa have been used to control the fluctuations of symptoms in this condition, raising the possibility that the pharmacokinetics of oral absorption are responsible for the phenomenon [57]. However, the successful use of the opioid antagonist naloxone in this condition suggests that there is an important interaction between other neural pathways and dopamine [68].

MOVEMENT DISORDERS AND ANAESTHESIA

Movement disorders are an occasional feature of anaesthesia. Tremor with spasticity may complicate recovery from general anaesthesia. Tremor may be marked during the early stages of development of extradural block. Muscle rigidity occurs with opioids in a dose-dependent or occasionally idiosyncratic fashion.

When the patient has an existing movement disorder, it is theoretically possible that interference with the control of movement by anaesthesia might worsen the condition. There has been little discussion of this possibility in the literature. For example, there have been several studies of the anaesthetic management of the patient with Huntington's chorea [16, 19, 45], but the influence of the anaesthetic on the movement disorder is not considered. Likewise, in Parkinsonism, existing articles mention the subject little, in this case limiting discussion to the hazards of butyrophenones and phenothiazines. Droperidol has been singled out as being particularly dangerous in the Parkinsonian patient [74] and responsible for drug-induced Parkinsonism in a normal patient [39, 60]. However, further examination of case reports of rigidity after treatment with droperidol shows that this drug is rarely the sole possible cause. There is only one report in which a movement disorder developed after administration of droperidol before any other drug was given [73]. Droperidol is usually given with the opioid fentanyl, and many case reports refer to fentanyl–droperidol combinations. (The combination fentanyl 50 μg ml^{-1} with droperidol 2.5 mg ml^{-1} was marketed as Innovar). Opioids themselves, even without droperidol, may precipitate rigidity. Is it possible, therefore, that what has been labelled as droperidol-induced Parkinsonism is the same as opioid-induced Parkinsonism? It is the aim of this article to discuss the evidence for the existence of opioid-induced Parkinsonism.

Evidence from the use of opioids in anaesthesia

Fentanyl is a popular drug for cardiac surgery, because of its lack of depressant effect on the cardiovascular system. If administered in sufficiently high dose, the use of an induction agent or supplementation with nitrous oxide or a volatile anaesthetic may be avoided. In these circumstances, there are several reports of muscle rigidity. An infusion of fentanyl 300 μg min^{-1} to a total dose of 50 μg kg^{-1} resulted in difficulty with mask ventilation [50]. Others have demonstrated rigidity at smaller total dose of fentanyl [14] and demonstrated hypercapnia [13] and increased pulmonary artery pressure [36] as a consequence of the difficulty in mask ventilation. Rigidity in the postoperative period after high dose fentanyl (up to 115 μg kg^{-1}) resulted in difficulty ventilating the lungs of patients in whom the trachea was intubated [12]. Rigidity can be abolished with a small dose of either naloxone 40 μg [12] or suxamethonium 3 mg [29].

Glottic closure has been claimed to be responsible for opioid-induced rigidity [2]. However, the occurrence of the phenomenon after tracheal intubation demonstrates that this cannot be a full explanation [12, 7].

The phenomenon is not limited to patients receiving large doses of fentanyl for cardiac surgery. It has been described postoperatively after an anaesthetic that contained a total dose of fentanyl 650 μg [7]. In this case the patient had awakened before rigidity was apparent. Another report described rigidity after infusion of fentanyl 250 μg, with patients awake and able to breathe normally on command [29]. Fentanyl-induced rigidity has been described after a modest dose of only 150 μg, following morphine premedication [61].

Electromyography (EMG) has been used to investigate opioid-induced rigidity. The amplitude of the H-reflex, a spinal reflex elicited by stimulation of the sensory fibres of a mixed nerve, increased in volunteers after administration of morphine, fentanyl, pethidine and, to a lesser extent, pentazocine [65]. However, the latency of the reflex was not affected, implying that opioids were acting at a supraspinal level to increase reflex activity. Opioids increased the activity of the abdominal wall EMG, as did nitrous oxide, a drug which precipitated rigidity when administered after opioid [22]. During induction of anaesthesia with alfentanil, synchronous phasic patterns of EMG activity were recorded from different muscle groups [4]. In this particular investigation, the onset of muscle rigidity was so rapid that it would have been confused with a tonic seizure had not simultaneous electroencephalogram recording suggested otherwise.

Static chest compliance and functional residual capacity (FRC) have been measured in volunteers after the infusion of Innovar. There were no control data for compliance and FRC before administration, but increase in these parameters after administration of suxamethonium at the end of the procedure was taken as evidence that Innovar caused a reduction in compliance and FRC [42].

Evidence from experiments with opioids in animals

It is clear that the concept of opioid-induced Parkinsonism has been suggested from animal experiments. The catalepsy observed in rats given large doses of morphine was described originally as analogous to Parkinsonism [44]. The dose used in such experiments was extremely high: Wand, Kuschinsky and Sontag [71] used doses of up to 10 mg kg^{-1}. It is interesting that naloxone and L-Dopa were equally effective in reducing the rigidity, and that an interaction between opioids and the dopaminergic system was strongly indicated. This interaction was investigated subsequently by the injection of specific opioid receptor agonists into the rat striatum [32]; in this way, the importance of the mu receptor was demonstrated. The direct application to the brainstem of a derivative of naloxone has enabled the action of opioids to be demonstrated in the nucleus raphe pontis [6].

Wand, Kuschinsky and Sontag [71] suggested that the action of morphine involved inhibition of dopamine release, that is, a presynaptic phenomenon. Investigations in rats with unilateral nigrostriatal lesions have suggested that postsynaptic receptors of the striatum may be affected also by morphine [37]. In these animals, morphine reversed the behaviour induced by the dopamine receptor agonist apomorphine.

In the light of these conclusions, the development of the MPTP-treated primate as a model for the study of Parkinsonism is interesting. The primate model might be used to investigate the relationship between opioids and dopamine. Numerous changes have been described in the endogenous opioid peptide profile in the MPTP primate [77]. There is a reduction in met-enkephalin in the substantia nigra, similar to that seen in the post-mortem brain of the patient with Parkinson's disease [67].

The action of other drugs on the opioid receptor: relevance of rigidity

The relationship between opioids and rigidity in man is highlighted further by the actions of nitrous oxide and ketamine. Nitrous oxide may precipitate muscle rigidity in subjects given opioids. Ketamine produces an increase in muscle tone. Is it possible that both these drugs and opioids act via similar mechanisms to affect the dopamine systems of the basal ganglia?

Nitrous oxide analgesia was antagonized by high doses of naloxone [75]. Prolonged exposure to nitrous oxide resulted in tolerance. Animals rendered tolerant to nitrous oxide exhibited a reduced concentration of opioid receptors in brainstem homogenates, suggesting that receptors are "down-regulated" [55]. Nitrous oxide displaced labelled dihydromorphine from binding sites in brain, suggesting nitrous oxide has a direct action on the opioid receptor [25].

Similarly, ketamine analgesia can be antagonized with naloxone. Ketamine was shown to compete for the same receptor as morphine in rat brain homogenate [63], and behaved in a manner similar to morphine in standard test systems for the opioid receptor [20]. However, it behaved differently from morphine with respect to the action of naloxone, which only partially inhibited its action [64], and after spinal cord transection [58]. It has been concluded that ketamine has some action at a spinal level and that it reacts with more than one type of receptor. However, the possibility that ketamine may interact with the opioid receptor to worsen the rigidity of Parkinsonism is not supported by a case report claiming that ketamine is a suitable anaesthetic agent for the patient with Parkinsonism [34].

Naloxone has been used in Parkinsonism, in treatment of the "on-off" syndrome. In high dose it reduced the period of time the patients spent in the rigid phase [68]. In addition it had a paradoxical action in reducing dyskinesia in the same patients. However, it did not affect the cardinal symptoms of Parkinsonism.

Other phenomena with rigidity: the neuroleptic malignant syndrome

The neuroleptic malignant syndrome is a rare complication of treatment with dopamine receptor antagonists, or abrupt withdrawal of L-Dopa [1,24]. Rigidity with hyperthermia progress to rhabdomyolysis and renal failure and the condition has an appreciable mortality. The anaesthetist must distinguish this condition from malignant hyperpyrexia, a condition which can be triggered in susceptible individuals by exposure to suxamethonium and anaesthetic vapours.

There has been discussion on whether or not the two conditions are related. Lotstra, Linkowski and Mendlewicz [49] have reported the successful use of suxamethonium for a course of electroconvulsive therapy in a patient who had recovered from the neuroleptic malignant syndrome. However, laboratory investigation does not entirely support the theory that the two syndromes are unrelated. Muscle biopsies from patients after malignant neuroleptic episodes demonstrate abnormal contractures with one of the test systems for malignant hyperpyrexia [11]. It is, of course, possible that this contracture represents the response of previously damaged muscle to the laboratory challenge.

When considering the role of opioids in modulating the activity of the dopaminergic system, the question arises of whether or not opioid-induced rigidity could precipitate neuroleptic malignant syndrome. In this respect it would be helpful if malignant hyperpyrexia and malignant neuroleptic syndrome could be demonstrated to be unrelated. Otherwise it is difficult to give a "safe" general anaesthetic to the patient with a suspected tendency to malignant hyperpyrexia.

The patient with Parkinsonism who does not receive L-Dopa before an anaesthetic that includes phenothiazine premedication and a large dose of an opioid may be considered, therefore, to be at risk of developing the neuroleptic malignant syndrome. Furthermore, differential diagnosis with malignant hyperpyrexia is difficult in these circumstances. The neuroleptic malignant syndrome, however, would not be expected to develop in a paralysed patient.

Involuntary movements after general anaesthesia

Post anaesthetic "shivering" has been confused with thermoregulatory shivering. Prys-Roberts [59] draws a distinction between the two, describing the former as tonic rigidity with a generalized coarse phasic tremor. Core temperature is frequently normal and piloerection, a characteristic feature of thermoregulatory shivering, is absent. The phenomenon is seen not only after halothane, the agent with which it is associated traditionally [66]. There are some interesting similarities and important differences between this postoperative rigidity and that of Parkinsonism. Unfortunately, there are no data specifically relating to the postoperative recovery of the patient with Parkinson's disease.

Johnstone [40] likened postoperative rigidity to decerebrate rigidity, describing clonus and exaggerated tendon reflexes. He noted that the rigidity was abolished by the amphetamine analogue methylphenidate, and concluded that this drug achieved its effect by arousing higher centres of the central nervous system.

In many patients, postoperative spasticity is of no importance and is transient. The use of i.v. methylphenidate (no longer available) is hardly justified for treatment of what is usually a self-limiting condition. However, postoperative spasticity may result occasionally in damage to teeth and grafts and may also result in airway obstruction. In addition, there is an increase in metabolic rate which may become critical in some patients [59].

In attempting to find an alternative drug for the treatment of postoperative rigidity, it should be considered that methylphenidate has a role in the treatment of Parkinsonism [52]. It is possible that other drugs used in Parkinsonism may be useful. Brichard and Johnstone investigated this possibility and could not demonstrate any benefit [8], but they did not use L-Dopa, which was unavailable at that time [M. Johnstone, personal communication]. More recently, it has been shown that the anticholinergic orphenadrine reduces pain by reducing postoperative muscle spasm [23].

Involuntary movements during extradural analgesia

Approximately 33% of labouring women "shiver" when extradural analgesia is administered [10]. Thermoregulatory mechanisms have been suggested as being responsible, as a result of increased heat losses, local cooling of the extradural space or i.v. infusion of cold fluids. However, it is not easy to obtain evidence for these hypotheses. The author's experience is that patients do not complain of cold, and "shiver" even if the local anaesthetic is warmed before administration. "Shivering" has been observed to develop many hours after the insertion of an extradural catheter and to stop after the extradural was discontinued [18]. The alternate administration of cooled and warmed solutions of local anaesthetic has been claimed to show the temperature dependence of shivering [69], but there are inadequate control data to prove the point.

The possibility exists, therefore, that what has been assumed to be thermoregulatory "shivering" with extradural analgesia is a different phenomenon. It is interesting to speculate that this particular movement disorder represents a loss of motor control, secondary to altered sensory input. If this were so, the patient with a pre-existing movement disorder such as Parkinsonism might be affected by an extradural block. However, no data exist on the subject.

PARKINSONISM AND ANAESTHESIA

Parkinsonism receives little attention in standard anaesthetic textbooks. Kadis discussed the hazards of dopamine receptor antagonists [41]. Hunter [38] considered that there was no need to modify anaesthesia in patients receiving L-Dopa, but Defalque and Musunuru were concerned about the effects of dopamine on the circulation [17]. The anaesthetic literature concerning the safety of anaesthesia in patients receiving L-Dopa [26, 54, 56] is of historical interest, having been written before the introduction of decarboxylase inhibitors into routine practice. The most recent review on the subject [9] put the anaesthetic management of the Parkinsonian patient in context, discussing the general problems of the elderly patient, but saying less about the special problems of the patient with Parkinsonism. The authors of another paper [62] expressed concern on the cardiovascular side effects of L-Dopa. These concerns were not warranted, for reasons just discussed.

The cardiovascular system

Postural hypotension has been demonstrated in Parkinsonism [30]. This hypotension was observed in patients before the start of L-Dopa therapy, and was not associated with any abnormality of the cardiovascular response to the Valsalva manoeuvre. Reports that L-Dopa has an arrhythmogenic potential were disputed [21]. Breathlessness and chest pain have been attributed to L-Dopa and antidopaminergic drugs [72].

Particular dangers of L-Dopa therapy before the era of decarboxylase inhibition included direct beta-receptor stimulation, release of noradrenaline and the replacement of noradrenaline stores with dopamine. Consequently, the anaesthetist of the day was cautioned against using halothane or cyclopropane [26]. Ngai showed that L-Dopa could be continued up to 6 h before operation without ill effect [54], but one of his patients, in whom L-Dopa was discontinued for a longer period, developed pulmonary oedema after operation [74]. This event was ascribed to withdrawal of L-Dopa, but there are other possible explanations.

The respiratory system

Aspiration of pharyngeal contents into the trachea is a possibility in the patient who has dysphagia resulting from Parkinsonism, and the dangers of this are compounded by excessive salivation and poor co-operation with chest physiotherapy. Chest wall rigidity and hypokinesia result in a restrictive pattern of respiratory deficit. Respiratory disability correlates with general disability in Parkinsonism. In a study of 23 patients, Neu [53] found that a reduction of ventilatory reserve volume and vital capacity and an increase in residual volume and functional residual capacity correlated with disability. This study also suggested that chronic airway obstruction resulting from parasympathetic hyperactivity could lead to emphysema.

Sleep apnoea has been described in post-encephalitic Parkinsonism. Where there was a history suggestive of encephalitis, patients with Parkinsonism were noted to have reduced variation of amplitude of ventilation, and reduced voluntary control of ventilatory rhythm [43]. L-Dopa has been blamed for disturbance of ventilatory rhythm in post-encephalitic Parkinsonism [27]. In this patient the irregular rhythm with apnoeic episodes resolved after cessation of L-Dopa.

In idiopathic Parkinson's disease, as opposed to post-encephalitic Parkinsonism, the occurrence of sleep-related ventilatory abnormalities is rarer and has been said to occur only in patients with autonomic disturbance [3]. It is manifest as irregular ventilatory rhythm during sleep, with episodes of obstructive apnoea and hypoxaemia. The resting rate of ventilation of the awake patient with Parkinson's disease was faster than that of the normal subject and decreased during sleep. This phenomenon was described as a consequence of intercostal muscle rigidity.

Preoperative assessment

This should take into account the considerations discussed above. The anaesthetist should note if medication has been continued during the hospital admission. Reasons for deterioration in neurological function after admission include omission of therapy and administration of antiemetics which act by antagonism of dopamine receptors; a diagnosis of an acute confusional state or dementia should not be entertained until the anaesthetist is satisfied that the Parkinsonism has been treated optimally. There is no reason to withhold L-Dopa before operation, and it should be given up to the time of surgery. L-Dopa is available for i.v. infusion, and is suitable for the patient who is unable to take oral medication. However, there is no i.v. formulation of a peripheral decarboxylase inhibitor.

Anticholinergic agents may help in reducing the volume of secretions and an anticholinergic bronchodilator such as ipratropium, theoretically, should relieve airways obstruction resulting from excessive parasympathetic activity. It is more logical to use an anticholinergic with a central action, such as atropine or hyoscine, than one which does not cross the blood–brain barrier, such as glycopyrronium.

The presence of autonomic dysfunction suggests the possibility of sleep-related ventilatory abnormalities, for which the postoperative ward should be prepared. A history of encephalitis has the same implications, although post-encephalitic Parkinsonism is extremely rare.

Tremor or dementia may result in difficulty in the performance of a local anaesthetic block or inadequate operating conditions without general anaesthesia.

Anaesthetic drugs and techniques

There is no absolute contraindication to the use of any particular technique of anaesthesia. However, the above account discusses potential problems if dopamine receptor antagonists are used and the possible dangers of the use of opioids in combination with nitrous oxide. The latter is mainly a theoretical consideration and, to the author's knowledge, has not yet been described as having adverse effects in Parkinsonism.

It is worth considering that opioids which act on the mu receptor may have the potential for precipitating rigidity. Thus there is no reason to suppose that pethidine, which has been recommended as an alternative to morphine [9], has any advantages. The possibility that kappa agonists, such as pentazocine, have less of an effect on muscle rigidity [65, 32] may be worth investigating, with a view to using these drugs as the analgesic of choice. However, there are side effects of pentazocine which might seriously offset its usefulness in elderly patients.

An alternative to the use of i.v. opioids is the use of extradural opioids. This technique may be able to reduce the effects of opioids on the basal ganglia. However, there is a risk that a drug such as morphine, which is poorly lipid soluble, could exert an effect on the brain after extradural administration. If extradural opioids are regarded as the method of providing analgesia, it would be logical to provide analgesia at a spinal level with a lipid soluble opioid such as fentanyl. There may even be a place for pentazocine at a spinal level. The use of extradurals with local anaesthetic, combined if necessary with a light general anaesthetic, is logical and confers many advantages.

There has been a case report in which hyperkalaemia after suxamethonium was recorded in a patient with Parkinsonism [28]. The patient was very ill, and undergoing cardiac surgery. The anaesthetist must weigh up the advantages of rapid onset of neuromuscular blockade in the dysphagic Parkinsonian patient against a known side effect of the drug. It is clear that some patients benefit from a rapid sequence induction of anaesthesia with appropriate measures to prevent pulmonary aspiration.

There has been a case report in which benefits are claimed from ketamine [34]. This is an interesting speculation as it conflicts with some of the theories advanced in this review. Clearly, there is a potential for further investigation.

It may be seen that there are many aspects of providing anaesthesia for the patient with Parkinsonism that lend themselves to simple clinical research. Such research will not only benefit the Parkinsonian patient undergoing anaesthesia, but may also help the neuroscientist who is attempting to unravel some of the pharmacological mysteries of this fascinating and perplexing condition.

SUMMARY

There are similarities between the motor disorder of Parkinsonism, the rigidity associated with the use of opioid drugs and the phenomenon of shaking during recovery from anaesthesia. Opioid receptors of the basal ganglia modulate activity of dopaminergic neurones. Opioid induced rigidity, therefore, may be a form of drug-induced Parkinsonism. This has implications for the anaesthetic management of the patient with Parkinsonism. Previous descriptions of the anaesthetic management of Parkinsonism have emphasized the cardiovascular complications of L-Dopa therapy, but have not discussed the importance of opioids.

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PULSE OXIMETRY DURING EXTRADURAL ANALGESIA FOR EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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SUMMARY

Exracorporeal shock wave lithotripsy (ESWL) may require immersion of the patient in water and extradural blockade for analgesia, which may both affect pulmonary and cardiovascular function and increase the likelihood of hypoxaemia. Twenty-four patients (ASA I–III) with extradural blockade and six healthy subjects were studied by pulse oximetry during immersion. Oxygen saturation (Sa_{O_2}) tended to decrease after induction of extradural analgesia. Immersion decreased Sa_{O_2} further, by up to 2% in healthy volunteers ($P < 0.05$) and 3% in patients ($P < 0.05$). In two patients with arteriosclerosis, an Sa_{O_2} of 92% was accompanied by arrhythmias which resolved after administration of oxygen.

Extracorporeal shock wave lithotripsy (ESWL) is used to disintegrate stones in the urinary tract by using focused shock waves. Extradural blockade may be required for the repeated sets of shock waves necessary to pulverize the stones [1]. The patient is treated in a semi-reclining body position during immersion in water. Functional residual capacity (FRC) and vital capacity (VC) are decreased, and intrapulmonary pressure and total work of breathing increased in normal subjects immersed up to the neck because of the hydrostatic pressure caused by immersion [2–4]. Cardiovascular changes may occur also [5], leading to variations in ventilation–perfusion relationships in the lungs and impaired gas exchange resulting in hypoxaemia.

The aim of this study was to evaluate the changes in oxyhaemoglobin saturation (Sa_{O_2}) with extradural blockade and immersion in water.

METHODS AND RESULTS

Fifteen patients (mean age 54 yr (range 30–80 yr)) of ASA grades I–II (group 1) and nine of ASA grade III (group 2) were studied during extradural blockade for ESWL. Six healthy volunteers (mean age 28 yr (range 22–37 yr)), were studied during immersion without extradural blockade. The study was approved by the Local Ethics Committee, and informed verbal consent was obtained.

The patients were premedicated with promethazine 25 mg and pethidine 50 mg i.m. approximately 1 h before induction of the extradural blockade. Isotonic fluid 5–10 ml kg^{-1} was given and an extradural catheter was placed in the L2–3 or L3–4 space. Mepivacaine 2% without adrenaline was given in a mean dose of 19 ml (range 14–23 ml), which was sufficient to achieve a blockade to approximately T7 (range T4–T8). The height of the blockade was assessed by ability for temperature discrimination. Heart rate was determined from the electrocardiogram, arterial pressure measured with a sphygmomanometer and rate of ventilation by observation. Sa_{O_2} was recorded continuously using a pulse oximeter (Nellcor-N 100) with a finger probe (model D-25). All shock wave treatments were performed with a Dornier lithotripter model HM3. The patients were placed in the ESWL chair with the arms above the head and were lowered into the water to the lower neck. Oxygen was not administered routinely. Sa_{O_2} was noted at the following times: supine in bed before induction of the extradural blockade; 20–30 min after injection of mepivacaine; after 5, 15 and 30 min of immersion; and supine in bed immediately after immersion.

Wilcoxon's test was used for statistical evaluation. The results are shown as mean (SEM)

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TABLE I. *Influence of extradural blockade and immersion in water on Sa_{O_2} during ESWL in patients, and immersion in volunteers. Mean (SEM) values and (range).* $*P < 0.05$ *relative to control values before treatment*

	Group 1 ($n = 15$)	Group 2 ($n = 9$)	Healthy volunteers ($n = 6$)
Supine in bed	98.9 (1.0) (97–100)	99.0 (0.7) (98–100)	99.7 (0.5) (99–100)
After extradural	98.3 (1.1)* (96–100)	98.8 (1.1) (97–100)	—
In water			
5 min	97.3 (2.1)* (93–100)	97.1 (1.2)* (96–100)	98.5 (1.0)* (97–100)
15 min	96.0 (1.8)* (93–98)	94.6 (1.1)* (92–96)	98.5 (1.0)* (97–100)
30 min	96.5 (1 7)* (93–99)	94.6 (1.1)* (92–96)	—
After immersion	99.1 (1.4) (96–100)	98.7 (0.7) (98–100)	99.5 (0.5) (99–100)

and range. $P < 0.05$ was considered statistically significant.

Sa_{O_2} tended to decrease after induction of extradural blockade, but was significant only in patients in group 1 ($P < 0.05$). Immersion was accompanied by a decrease in Sa_{O_2} in the volunteers ($P < 0.05$) and in both groups of patients ($P < 0.05$) (table I).

There was no difference in rates of ventilation either between the groups or before and during immersion.

Two of the patients in group 2 developed ventricular extrasystoles when Sa_{O_2} was decreased (92%); this resolved when oxygen was administered by facemask.

Arterial pressure did not decrease below 80% of preanaesthetic values in any patient or volunteer.

COMMENT

A slight decrease in Sa_{O_2} was observed in healthy subjects during immersion. In the two patient groups a tendency towards a decrease in Sa_{O_2} was found after extradural blockade ($P < 0.05$ in group 1) and this was accentuated by immersion. These findings tend to confirm earlier studies which demonstrated an adverse effect of immersion on lung function.

Two of the patients in group 2 (ASA III) had frequent ventricular extrasystoles during immersion. The arrhythmias may have been related to arterial hypoxaemia, as they resolved when oxygen was administered. In both patients Sa_{O_2} was decreasing before the extrasystoles were noted.

The reductions in Sa_{O_2} in group II may be related to impaired ability to compensate for circulatory changes secondary to vascular disease, resulting in disturbed ventilation–perfusion relationships. Premedicant drugs may impair respiration and may have contributed to the reductions in Sa_{O_2} in the patient groups. However, the Sa_{O_2} values before extradural blockade and immersion did not differ from those of the volunteers, suggesting that the effect was minimal. It is recommended that respiration and oxygenation are monitored during ESWL, and supplementary oxygen be given to high-risk patients.

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ILIOINGUINAL NERVE BLOCKADE FOR ANALGESIA AFTER CAESAREAN SECTION

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SUMMARY

Bilateral ilioinguinal nerve blockade was performed, using 0.5% plain bupivacaine 10 ml to each side, in 13 patients having elective Caesarean section under general anaesthesia. Pain scores and requirement for postoperative analgesia were compared with 13 patients in a control group. Pain scores were less in the block patients at all times during the first day after operation, with the exception of 12 h. There was an increased time from the patient's recovery from anaesthesia to the first injection of opioid in the block group. In the control group, patients required more analgesia in the first 24 h after surgery compared with patients having ilioinguinal nerve blockade. There were no observed adverse effects following nerve blocks.

Lower segment Caesarean section performed through a Pfannenstiel incision is associated commonly with pain in the postoperative period [1]. Many Caesarean sections are performed using regional analgesia, one of the advantages of which is that some degree of residual analgesia persists into the postoperative period. However, general anaesthesia for Caesarean section is still widely used. Analgesia following this procedure is provided usually by i.m. injections of opioid analgesics. Although simple, this method has been shown to be one of the least efficacious [2], and may produce side effects such as nausea, vomiting, dizziness and respiratory depression.

Bilateral blockade of the ilioinguinal and iliohypogastric nerves at the level of the anterior superior iliac spine produces analgesia covering the dermatome supplied by the first lumbar nerve in its distal distribution [3]. The Pfannenstiel incision lies within this dermatome. It is possible, therefore, to provide analgesia of the anterior abdominal wall following this incision using the above technique. This does not abolish pain arising from visceral structures, as these have a different nerve supply.

METHODS AND RESULTS

The study was approved by the local Ethics Committee. Twenty-six patients undergoing elective Caesarean section who wished to have a general anaesthetic were approached and written informed consent obtained. Patients were allocated randomly to either a control group or the group ($n = 13$) receiving bilateral ilioinguinal nerve blockade. There were no significant differences in height, weight, parity or in postoperative measurements of arterial pressure, heart rate or rate of ventilation between the two groups.

A standard anaesthetic technique was used. Antacid prophylaxis was achieved with ranitidine 150 mg by mouth, two doses in the 12 h before surgery and 30 ml of sodium citrate 0.3 mol litre^{-1} immediately before induction of anaesthesia. Following preoxygenation for 4 min, a rapid sequence induction with thiopentone 4 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} was administered. Cricoid pressure was applied and the trachea intubated with a tracheal tube of appropriate size. Neuromuscular blockade was maintained with vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained using nitrous oxide and enflurane in oxygen in appropriate concentrations. At delivery all patients received oxytocin 10 unit followed by fentanyl 100 µg.

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TABLE I. *Pain Scores (Mean values (range))*

	Time (h)				
Group	0	4	8	12	24
Control	7.15 (4–10)	5.30 (1–7)	5.12 (2.5–7)	4.08 (1–6)	4.00 (2–6)
Blockade	4.08 (2–7)	3.31 (1–7)	3.12 (2–5)	3.00 (1–5)	2.69 (2–6)
P	< 0.01	< 0.01	< 0.01	ns	< 0.01

Bilateral ilioinguinal nerve blockade was performed on patients allocated to the nerve block group at the end of surgery before antagonism of neuromuscular blockade. Using the technique described by Eriksson [4], a 21-s.w.g. needle was positioned, but a reduced volume (10 ml) of the more concentrated 0.5% plain bupivacaine was used. Residual neuromuscular blockade was antagonized with a mixture of atropine and neostigmine.

When patients were judged to have recovered from the anaesthetic sufficiently to co-operate with the study, measurements were made of heart rate, arterial pressure and rate of ventilation (0 h). Pain scores were recorded using a 10-cm linear analogue [5]. All observations were made by one of the authors who was unaware of the analgesic regimen. Further observations were made at 4, 8, 12 and 24 h after surgery. All patients were prescribed papaveretum 10 mg/m^2 body surface area and perphenazine 5 mg as an antiemetic. Time to the first dose and the total dose of papaveretum were rewarded.

Demographic data and cardiovascular data were analysed using Student's *t* test. All other data were subjected to the Wilcoxon rank sum test. $P \leqslant 0.05$ was considered statistically significant.

Pain scores were lower at all times during the study in the patients receiving ilioinguinal nerve blockade (table I). The differences were highly significant ($P < 0.01$) at times 0, 4, 8 and 24 h. At 12 h the pain score was not significant.

In the first 30 min after surgery 10 patients in the control group received an initial dose of papaveretum. In the same period only one patient in the ilioinguinal nerve block group received papaveretum.

At the end of the second hour after operation all patients in the control group had received the first dose of papaveretum, compared with five patients in the ilioinguinal nerve block group. At 24 h one patient in the control group had received two injections of papaveretum, seven patients four injections, three five injections and two six (a total of 57). In the study group three patients received no opioid, five patients one injection, two received two injections, two three injections, and one had four, this being the same patient as required the first dose within 30 min of recovery (a total number of 19 injections). The quantity of papaveretum administered per patient in 24 h was 51.5 mg m^{-2} (range 27–76.9) in the control group and 16.75 mg m^{-2} (range 0–47.05) in patients having ilioinguinal nerve blocks ($P < 0.01$).

COMMENTARY

The operation of Caesarean section involves dissection of deep tissues in the pelvis. It would be expected, therefore that, while providing analgesia of the skin and deeper layers of the anterior abdominal wall, ilioinguinal nerve blockade would not provide visceral analgesia. This appears to be the case, as all patients in the present study experienced some pain at all times during this study, including three patients who reported some pain but did not require additional analgesia.

Ilioinguinal nerve blockade is a simple regional technique which takes little time to perform. The method is safe provided the permitted maximum dose of local analgesic agent is not exceeded, and care is taken to ensure asepsis and avoidance of intravascular injection [6]. There were no complications which could be attributed to nerve blockade in this study. We have shown that the technique reduces pain during the first day after operation and decreases by a significant amount the requirement for additional postoperative analgesia.

In conclusion, we suggest that, when general anaesthesia is indicated for lower segment Caesarean section using a Pfannenstiel incision, bilateral ilioinguinal nerve blocks improve the quality of postoperative analgesia.

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VARIATIONS IN THE GLIDING CHARACTERISTICS OF 10-ML PLASTIC SYRINGES USED TO LOCATE THE EXTRADURAL SPACE BY "LOSS OF RESISTANCE" TECHNIQUES

S. R. W. BRICKER AND P. COLEMAN

SUMMARY

The gliding characteristics were evaluated of 10-ml plastic syringes used to identify the extradural space by "loss of resistance" techniques. This was undertaken quantitatively, by measuring the force necessary to depress syringe plungers, and qualitatively, by examining travel characteristics in terms of the force applied, together with the rate and uniformity of plunger travel. An important cause of inadvertent dural puncture is the use of syringes with plungers that do not move freely; this study has identified wide variations between makes which may be of particular relevance to anaesthetists inexperienced in techniques of extradural analgesia.

Numerous methods of locating the extradural space have been described; however, the "loss of resistance" to injection technique described first by Sicard and Forestier in 1921 [1] remains popular. Inadvertent dural puncture during the performance of extradural block is an important complication, and intrinsic resistance to free movement of the plunger of the syringe may be contributory [2]. Freely moving syringes are, therefore, essential for success [3,4]. It is mainly for this reason that, traditionally, glass syringes have been favoured, but disposable plastic syringes are a cheap and convenient alternative. The purpose of this study was to evaluate the gliding characteristics of six brands of plastic syringe.

MATERIALS AND METHODS

Ten-millilitre plastic syringes from six manufacturers were assessed: Braun "Omnifix", Becton–Dickinson (B–D) "Plastipak", Gillette "Sabre", Sherwood "Monoject", Steriseal "Poly-Vu" and Terumo "Terumo 10 ml". At least two different batches of each syringe were examined, and for completeness a number of glass syringes in addition to the Portex "Loss of Resistance Device" were assessed.

A simple apparatus was devised to measure the force necessary to depress the plunger of a syringe from various points along its barrel. Each syringe was supported vertically with a Tuohy needle (Steriseal) attached to the nozzle, which pointed downwards. A light horizontal bar surmounted the extended plunger and from this was suspended a container into which water could be added via a burette (fig. 1). Sufficient fluid was added to initiate movement of the piston with complete travel down the barrel. In those tests in which the syringes were filled with saline, the fluid expelled as the plunger moved was diverted away from the container. The measured volume of water was added to the weight of the dry rig, thereby allowing determination of the total force applied. All experiments were carried out at room temperature (20–21 °C).

Each syringe was removed from its sterile pack, the plunger extended to the 10-ml mark and the force required to depress it fully measured. The piston was then worked back and forth the full length of the barrel to the 10-ml mark and the test repeated. This manoeuvre reflected the clinical

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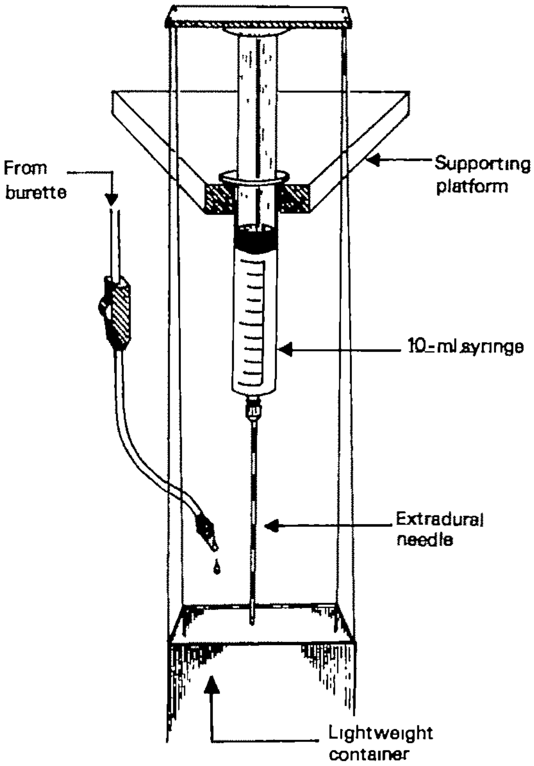

FIG. 1. Diagram of apparatus.

practice of moving the plunger a number of times in order to "free" its travel. The piston was tested from halfway down (at the 7–8 ml mark depending on the make of syringe) and from two-thirds (at the 4–5 ml mark) of the way down the barrel. The empirical choice of these points followed the consideration that, before performing an extradural block, most anaesthetists would extend the plunger approximately to these points, according to the size of their hands.

Measurements were repeated with different syringes which had been filled with 0.9% sodium chloride.

The descent of the plunger from the 10-ml mark was timed and its uniformity of travel assessed. The force applied and the speed and uniformity of travel were combined to allow a qualitative assessment of the syringes under test. The force applied was defined as "high" or "low" according to its relationship to the median value for all syringes in that particular test. Movement of the plunger was defined as "rapid" if travel was completed within 2 s and "slow" if it took longer than 5 s. These values were chosen because, apart from a small number of saline-filled syringes, none was actually timed at between 2 and 5 s, and this appeared to be a natural division which reflected two populations. Plunger travel was described broadly as "uniform" or "non-uniform" with syringes in which the piston stuck delineating a third category. Such a system helped definition of the characteristics of an individual syringe by allowing it to be placed into one of 12 possible groups, but this was regarded as too unwieldy to be of clinical value. For the purposes of a more useful qualitative assessment, therefore, each syringe was put into one of three groups. The "best" group was defined as that in which slow and uniform travel was initiated by a low force, or in which the syringe plunger moved freely without discernible resistance. The "worst" was defined as that in which rapid and uneven travel was initiated by a high force, or in which plunger travel was arrested, to be restarted only by the application of a further high force. It was considered that such syringes had an intrinsic resistance which could mask the loss of resistance of the tissues and thereby increase the likelihood of dural puncture. Syringes which did not satisfy the criteria for inclusion in either of these two groups were placed into an "intermediate" group. This category contained, for example, syringes in which slow, even travel required a high force, in addition to syringes in which rapid, uneven travel was initiated by a low force. Also included were those few syringes which were timed at between 2 and 5 s. It was felt that these and other possible combinations did not lend themselves to obvious ranking.

It was not assumed that the data were distributed normally, therefore they were analysed by means of multiple non-parametric statistical tests. Wilcoxon's rank sum test for paired data was used to compare the forces applied at different points on an individual syringe. Differences between groups of syringes were compared using the Mann–Whitney *U* test, for which two-tailed *P* values were obtained.

RESULTS

Different batches of all syringes were evaluated, but it was only in the case of Gillette Sabre that there was any difference ($P < 0.005$ when air-filled syringes were compared, $P < 0.05$ in the other two tests), and so results for both sets are given.

TABLE I. *Force (median and range) required to depress syringe plunger from 10 ml.* $^{*}P < 0.05$; $^{***}P < 0.001$; $^{****}P < 0.005$

Syringe type	Force (air) (N)	Force (NaCl) (N)
Sherwood Monoject $(n = 35)$	1.30 (0.55–2.77)	0.45 (0.31–1.26)***
Terumo $(n = 35)$	1.59 (0.92–3.12)	1.79 (0.51–3.97)
Becton–Dickinson Plastipak $(n = 35)$	1.74 (0.94–3.86)	1.60 (0.49–2.77)
Steriseal Poly-Vu $(n = 35)$	2.89 (1.82–6.69)	1.98 (0.72–6.69)****
Braun Omnifix $(n = 35)$	3.09 (1.93–9.34)	3.85 (2.76–12.48)****
Gillette Sabre (batch 1) $(n = 15)$	4.74 (1.92–13.61)	2.88 (1.41–4.81)*
Gillette Sabre (batch 2) $(n = 15)$	13.23 (4.90–17.95)	4.60 (1.69–8.81)***
Glass Rocket and Chance $(n = 16)$	4.73 (0.17–19.41)	3.43 (0.17–12.36)
Portex LoR device $(n = 15)$	0.43 (0.17–0.71)	0.06 (0.05–0.18)***

The addition of 0.9% sodium chloride resulted in a marked decrease in the force applied to Sherwood and to both batches of Gillette syringes ($P < 0.01$), while it increased the force needed to move the plunger of Braun syringes ($P < 0.01$). With the remaining makes there was minimal change. Overall, Sherwood Monoject required the application of less force than the other syringes tested ($P < 0.001$). There was no difference between B–D and Terumo syringes, which required less force than the remaining types ($P < 0.01$) (table I). The addition of saline to syringes did not alter this ranking; Sherwood syringes again required the least force ($P < 0.0001$).

The effect on force of working the syringe plunger back and forth in order to free its travel had little effect on Sherwood, Terumo, B–D or Steriseal syringes, but did improve travel in the case of Gillette and the glass syringes tested ($P < 0.01$). With Braun Omnifix, however, an attempt to improve travel characteristics by working the plunger was accompanied by a substantial increase in the force exerted ($P < 0.001$).

TABLE II. *Force (median and range) before and after working the syringe plunger to free its travel.* $^{**}P < 0.01$; $^{***}P < 0.001$

Syringe type	Before working (N)	After working (N)
Sherwood $(n = 35)$	1.30 (0.55–2.77)	0.99 (0.52–1.98)
Terumo $(n = 35)$	1.59 (0.92–3.12)	1.73 (1.07–3.57)
B–D $(n = 35)$	1.74 (0.94–3.86)	1.78 (0.81–3.48)
Steriseal $(n = 35)$	2.89 (1.82–6.69)	2.70 (1.21–6.65)
Braun $(n = 35)$	3.09 (1.93–9.34)	4.95 (2.38–15.81)***
Gillette (batch 1) $(n = 15)$	4.74 (1.92–13.61)	3.73 (1.52–5.78)**
Gillette (batch 2) $(n = 15)$	13.23 (4.90–17.95)	5.10 (2.65–8.88)***
Glass $(n = 16)$	4.73 (0.17–19.41)	2.28 (0.17–8.73)***
Portex LoR $(n = 15)$	0.43 (0.17–0.71)	0.18 (0.17–0.49)***

TABLE III. *Force (median and range) required to depress plunger from different points along syringe barrels after working piston. †Determinations made without the syringe plunger being worked.* *$P < 0.05$; **$P < 0.01$

Syringe type	From 10 ml (N)	From 7–8 ml (N) (halfway)	From 4–5 ml (N) (two-thirds)
Sherwood ($n = 21$)	1.06 (0.52–2.14)	0.97 (0.77–1.99)*	0.99 (0.76–2.18)
Terumo ($n = 21$)	1.56 (1.07–4.41)*	1.71 (1.11–4.04)	1.67 (1.10–4.43)
B–D ($n = 21$)	1.87 (0.81–3.61)	1.51 (0.76–2.26)*	1.53 (0.70–2.33)
Steriseal ($n = 21$)	2.43 (1.21–4.89)	1.67 (0.55–3.92)	1.61 (0.78–4.62)**
Braun ($n = 21$)	4.42 (2.38–15.81)	4.22 (1.78–13.76)	3.28 (1.60–10.52)*
Braun† ($n = 21$)	2.79 (1.93–5.49)	3.38 (1.73–7.58)	3.16 (2.01–5.72)
Gillette (batch 1) ($n = 15$)	3.73 (1.52–5.78)*	4.76 (1.36–7.88)	4.01 (1.90–8.51)
Gillette (batch 2) ($n = 15$)	5.10 (2.65–8.88)**	9.29 (3.23–13.88)	9.62 (3.52–14.42)
Glass ($n = 16$)	2.28 (0.17–8.73)	1.77 (0.17–11.13)	1.38 (0.17–12.94)**

Working the syringe piston had minimal influence on the ranking: Sherwood still required the least force ($P < 0.001$), but glass syringes joined B–D and Terumo in requiring less force than other makes ($P < 0.05$) (table II).

In each of the three tests the plastic and glass syringes required the application of greater forces than the Portex "Loss of Resistance" device ($P < 0.0001$).

Table III outlines the forces applied at different points along the barrels of a proportion of the syringes tested. There were wide variations between makes. The point at which the least force needed to be applied was halfway down the barrel

TABLE IV. *Travel characteristics of syringes (numbers in each group). Best = Slow (> 5 s), even travel initiated by low (< median) force. Worst = Rapid (< 2 s), uneven travel initiated by high (> median) force, or plunger travel arrested after application of high force. Intermediate = All other groups: e.g. slow, uneven travel initiated by high force; rapid, uneven travel initiated by low force*

	Best		Intermediate		Worst	
Syringe type	Air	NaCl	Air	NaCl	Air	NaCl
Sherwood ($n = 35$)	33	35	2	0	0	0
B–D ($n = 35$)	22	27	13	8	0	0
Terumo ($n = 35$)	29	24	2	8	4	3
Steriseal ($n = 35$)	6	18	27	17	2	0
Gillette (batch 1) ($n = 15$)	2	2	10	12	3	1
Gillette (batch 2) ($n = 15$)	0	1	11	14	4	0
Braun ($n = 35$)	2	3	16	30	17	2
Glass ($n = 16$)	3	5	5	2	8	9
Portex LoR ($n = 15$)	12	15	3	0	0	0

TABLE V. *Influence on travel characteristics of "freeing" the syringe plunger*

	Best		Intermediate		Worst	
Syringe type	Before	After	Before	After	Before	After
Sherwood ($n = 35$)	33	34	2	1	0	0
B–D ($n = 35$)	22	25	13	10	0	0
Terumo ($n = 35$)	29	28	2	5	4	2
Steriseal ($n = 35$)	6	7	27	27	2	1
Gillette (batch 1) ($n = 15$)	2	2	10	10	3	3
Gillette (batch 2) ($n = 15$)	0	0	11	13	4	2
Braun ($n = 35$)	2	0	16	17	17	18
Glass ($n = 16$)	3	4	5	6	8	6
Portex LoR ($n = 15$)	12	15	3	0	0	0

in the case of Sherwood and B–D syringes ($P < 0.05$), was at 10 ml for Terumo and Gillette ($P < 0.05$), and was two-thirds of the way down for Steriseal, Braun and glass syringes ($P < 0.01$, $P < 0.05$ and $P < 0.01$, respectively).

Tables IV and V list the numbers of syringes which fell into the best, worst and intermediate groups. Only one of the Sherwood syringes tested failed to satisfy criteria for the best group, with none appearing in the worst. No B–D syringe appeared in this latter group, although rather more fell into the intermediate group. Of the other makes assessed, all had some syringes which could mimic loss of resistance according to the criteria defined above, Braun and glass performing least well in this regard. In general the addition of saline appeared to improve travel characteristics: this was true especially of Steriseal and Braun, but glass syringes were an exception. Similarly, the manoeuvre of working the plunger improved travel characteristics, and in particular decreased the number of syringes falling into the worst category. In all tests the Portex device came out well, with most appearing in the most favourable group and none falling into the worst.

DISCUSSION

The mishap of accidental dural puncture may have grave sequelae in rare cases; at the least it is an embarrassment which, in many obstetric units, may commit a mother to instrumental delivery. It is therefore a complication to be avoided. Bromage has written that "... sticky syringes are one of the commonest causes of accidental dural puncture" [2], and he is not alone in emphasizing the importance of using high quality apparatus to detect the loss of resistance which, although quite definite, is of small magnitude [3,5]. It is when that apparatus is considered in detail that difficulties arise. What are the properties of the ideal syringe used for this purpose? In the present evaluation of syringes, certain assumptions have been made, with the justification that they reflect clinical practice; it is recognized, nevertheless, that the classification into "best", "worst" and "intermediate" groups may seem arbitrary. However, we would argue that it seems reasonable to favour a syringe with a plunger that moves slowly and evenly in response to minimum force, and it seems prudent to avoid a syringe in which the plunger "gives" suddenly after the exertion of a higher force.

Do our findings allow a rational choice of equipment to be made? Of all the apparatus tested the Portex Loss of Resistance Device appeared to perform the best. With the barrel filled with 0.9 % sodium chloride, the piston in 11 of the 15 devices tested descended slowly and evenly under the weight of the plunger alone (only 5 g). It should be noted, however, that this apparatus is not described as a syringe, because it does not conform to the British Standard Specification [6], which includes a stringent leakage test for both air and fluid, and a tight seal between piston and barrel may prevent optimal gliding characteristics. Three of the glass syringes tested also had pistons which ran freely under the weight of the plunger alone (17–18 g), but a high proportion of those evaluated either stuck or required the application of a large force to initiate travel. In the most extreme case, this exceeded by a factor of almost 400 the force required to depress the plunger of the Portex device. Although a glass syringe may perform well when used to identify the extradural space, these results suggest that there is a wide variation between glass syringes which renders a proportion of them particularly unsuitable for that purpose. We examined reusable glass syringes which were supplied after repeated autoclaving by the hospital sterile supplies department. It should be recognized that new syringes, and in particular those which are presented as part of specifically designed "extradural packs", might well be more satisfactory.

Variation in performance also characterized some of the types of plastic syringe tested, and it may be that consistency and predictability are the most important features in seeking the most suitable apparatus. According to this argument, saline-filled Braun or Gillette syringes, 95% of which fell into the intermediate group, might be preferable to those makes such as Terumo or Steriseal in which syringes were categorized into both the best and the worst groups. Becton–Dickinson performed consistently better than these latter, but were less impressive than the Sherwood syringes, all but one of which could be placed in the most favourable group.

The use of saline rather than air appeared consistently to improve the travel characteristics of syringes, and this was true especially of Steriseal and Braun.

Not unexpectedly, an attempt to free the plunger by repeated movement improved the gliding properties of those syringes with greater intrinsic resistance (Braun, Gillette and glass), but in the case of the Braun syringes this manoeuvre increased the force needed to be applied. It had little effect on the other syringes evaluated.

This study aimed to evaluate plastic syringes which might be used in the detection of the extradural space by loss of resistance in a way which reflected the clinical situation, and which would permit a rational choice to be made. It did not, however, attempt to offer explanations for differences between syringes. The Portex Loss of Resistance Device is designed specifically for the purpose and, on the evidence of the sample tested, approaches the ideal more nearly than any other of the apparatus tested. Currently, however, each costs £1, compared with 5p for 10-ml plastic syringes. Of these plastic syringes, Sherwood Monoject were the most satisfactory according to our criteria, with Becton–Dickinson Plastipak performing marginally less well.

This was a bench study, albeit clinically orientated, and we should not wish to overstate the applicability of the findings. Nonetheless, we conclude that the study has identified differences between syringes which, while they may be of only modest significance to experienced anaesthetists, may make it much more difficult for the inexperienced to acquire skill and confidence in the performance of extradural blocks. Not every dural puncture results from the use of an unsuitable syringe, but if trainees and others could be presented with optimal equipment, an important contributory factor might be eliminated.

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COMMENTARY

GUEST REVIEWERS FOR 1988

Each manuscript submitted to *British Journal of Anaesthesia* is reviewed by members of the Editorial staff, and also by individuals with particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaesthesia. Consequently, acceptance for publication is based on the views of two or more individuals as to originality, validity and clinical relevance of the information presented.

The Editor would like to acknowledge the significant contributions made by the undernoted individuals who, in addition to the members of the Editorial Board, reviewed manuscripts during 1988.

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CORRESPONDENCE

HALOTHANE: PLUS CA CHANGE, PLUS C'EST LA MEME CHOSE [1]

Sir,—The correspondence [2, 3] between Professors Asscher and Spence indicates that relationships between the Committee on Safety of Medicines (C.S.M.) and the specialty of anaesthesia have not improved over the past 15 years. In 1974 Dr Inman and Professor Mushin published an analysis of reports to the C.S.M. of jaundice after repeated exposure to halothane [4]. At the same time the C.S.M. circulated a letter to all doctors, dentists and pharmacists within the United Kingdom, drawing attention to the article. Both publications were criticized severely, essentially on the grounds that, although the conclusions might be correct, insufficient data were presented [5]. In addition, the C.S.M. was petitioned by the Anaesthetic Research Society, the Association of Professors of Anaesthesia (with one notable exception) and the Anaesthetists' Subcommittee of the Central Committee for Hospital Medical Services to circulate a moderated version of their document after due consultation with the specialty. No such consultation or publication occurred.

In the intervening years, particularly in North America, the use of halothane has declined dramatically [6]. Factors responsible include availability of other volatile agents, anxiety over pollution of the operating theatre and the possible threat of litigation if unexplained hepatitis followed halothane anaesthesia; it is of interest that no case has come to trial, although there are alleged out-of-court settlements. It is in the area of perceived litigation that the C.S.M. has contributed to the downfall of halothane.

The C.S.M. might be forgiven for its conduct if anaesthetic safety has been enhanced by a reduction in halothane usage. However, this may not be the case. For example, respiratory depression, which occurs with inappropriate use of opioids by anaesthetists to avoid the "dilemma" of volatile anaesthetics, causes more problems than have ever resulted from the use of halothane. These patients do not normally attract great attention, even though some may not survive, and as there are no dramatic changes, for example jaundice, the cases are not reported to the C.S.M..

I support Professor Spence's plea for consultation between the C.S.M. and our specialty, on all aspects of possible anaesthesia-related drug interactions. However, from the historical perspective, I am not sure this will occur.

L. Strunin
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BOOK REVIEWS

Regional Anaesthesia. By M. Zenz, C. Panhans, H.C. Niesel and H. Kreuscher. Published (1988) by Year Book Medical Publishers/Wolf Medical. Pp. 243; indexed; illustrated. Price £73.50.

There has been a proliferation of textbooks on regional techniques in recent times. Does this one offer any significant advantage over its competitors? Nineteen contributors and a translator have combined to produce *Regional Anaesthesia* which originates from a German text produced in conjunction with Astra Pharmaceuticals. Indeed, many will recognize the illustrations from the pocket-size booklet distributed by that company.

Two sparse chapters introduce the book: the first outlines, with unsubstantiated claims, the advantages of regional over general anaesthesia; the second enumerates complications of regional anaesthesia. Neither is referenced. The main text is classified into Surgery, Obstetrics, and Pain Therapy. Surprisingly, one needs to look in this final section for intercostal nerve block.

The book is produced lavishly on good quality paper and is illustrated beautifully, with photographs of excellent colour balance and precisely-drawn diagrams which complement the photographs—frequently appearing in parallel in order to emphasize anatomy. As stated in the preface, each chapter is intended to stand on its own; as a result there is much unnecessary repetition of material. For example, assessment for anaesthesia recurs, and there are no fewer than 20 illustrations of equipment which varies only in minor detail from chapter to chapter. It is clear that the chapters are intended as a practical guide: little discussion of the merits of differing techniques is found and references appear to standard works such as Moore and Bromage. However, the text is not devoid of errors and there are some surprising omissions. Many references are to German sources, and recommended agents are American, or transatlantic spelling is used.

This is a very nicely presented recipe book, but may not be advisable as the sole text for trainee anaesthetists who demand a more discursive approach. At this price, more than twice that of a recent British book, it is questionable if it offers advantages over its competitors.

D. Fell

A Tribute to Professor Sir Robert Macintosh for his 90th Birthday. Souvenir Volume. Edited by W. D. A. Smith and G. M. C. Paterson. Published by The Royal Society of Medicine, London. Pp. 45; illustrated; not indexed. Price £7.95.

This handsome little book, so elegantly printed and bound, was produced to commemorate the 90th birthday of Professor Sir Robert Macintosh. It contains a series of historical reviews from members of Sir Robert's department, together with greetings from the Anaesthetic Section of the Royal Society of Medicine, the Association of Anaesthetists, the Faculty of Anaesthetists and the European Academy of Anaesthesia.

Admirers of Sir Robert may be disappointed to find that their favourite anecdotes are missing from the text, and it would be easy to suggest what should have been included and what could have been omitted. In truth, in some instances we learn more about the contributors than about Sir Robert; but it is no matter, on this particular occasion, the substance of text is of secondary importance. What is important is the great demonstration of respect and affection shown for Sir Robert by anaesthetists world-wide, most of whom, and especially those with a sense of history, will wish to possess a copy of this book. It is to be hoped that a sufficient number have been printed to make this possible. If not then perhaps a reprint is indicated, in which case the mis-spelling of Dr Parry Brown's name could be corrected.

J. P. Payne

Foundations of Obstetric Anaesthesia 1987. Edited by B. M. Morgan. Published by Farrand Press, London. Pp. 309. Price £19.80.

This multi-authored book is derived from the justly renowned course which Dr Morgan has organized at Queen Charlotte's Maternity Hospital each autumn for several years. Some of the chapters reflect this origin, tending to resemble essays rather than treatises.

The structure of the book is rather odd. Chapters relating to the basic sciences (for example, physiology and pharmacology) appear half-way through rather than, as is more traditional, at the beginning to set the scene. However, I have a more important criticism which might puzzle readers inexperienced in obstretic anaesthesia, namely that the volume is grossly unbalanced in favour of extradurals, a topic which occupies the first 30% of the book and other pages thereafter. The history of extradural analgesia alone is recounted (in a fine review by Andrew Doughty). There is a somewhat perfunctory, and at times misleading, dismissal of all other forms of pain relief and additional support for the mother in labour. (Since when has promazine administered during labour been declared to cause babies to remain sleepy for many days? Surely responsible clinicians are no longer concerned by the prospect that transplacentally derived pethidine might on occasion, cause a modicum of central nervous system depression of the infant? How many of us support the contention that pethidine should not be given to a mother who is likely to come to Caesarean section?)

Extradural blocks do not comprise the universal technique of obstetric anaesthetic practice, and a book which seeks to be authoritative should not present them as such. Donald Moir, in his otherwise characteristically admirable account of extradural anaesthesia for Caesarean section, indicates that, if a "skilled anaesthesist can prevent or treat" the complications of an extradural block, thus preventing a fatality, this individual should also be able to avert the complications associated with general anaesthesia and hence in that regard alone, the one choice has no advantage over the other.

I was concerned that some statements do not match with my own observations, practice or understanding. Examples include: after an inadvertent dural tap the patient should remain prone for 24–36 h, and syntometrine should not be given; top-ups should be given only by the anaesthetist if it is anticipated that delivery eventually occurs by Caesarean section or forceps, and in cases of breech presentation or multiple pregnancy (that would apply to 50–60% of our labouring mothers); it is not "now well established that gastric emptying is delayed in labour", unless the mother is exhausted or has received opioid analgesia; the uterine spiral arteries are not "rich in α-receptors and capable of vasoconstriction" except among mothers with pre-eclampsia (and possibly the diabetic mothers)—in all other cases secondary trophoblastic invasion has occurred and the neuromuscular coat of the spiral arteries has been replaced by a fibrous sheath; the contention that extradural block for Caesarean section of a pre-eclamptic mother is absolutely contraindicated is reminiscent more of U.S. than of British practice.

I was diappointed that in the chapters on neonatology there was no mention of the possibility (assuming increasing medico-legal importance) that a considerable proportion of the cases of neurological dysfunction among children have their origin in some "silent" ante-natal complication.

Gillian Hanson's chapter on shock in obstetric patients is a model of clarity and sound advice. The procedure she presents for the treatment of obstetric haemorrhage should be posted in every obstetric unit—I have certainly adopted it for ours.

There is, unfortunately, a plethora of typographical or spelling errors (I counted 65), and errors of grammar and syntax.

In summary, my general verdict is that this is an interesting publication, well worth reading, but it is not a text-book of obstetric anaesthesia and analgesia.

J. Selwyn Crawford

Preanesthetic Assessment 1. Edited by E. A. M. Frost. Published by Birkhäuser, Boston, U.S.A. Pp. 305; indexed; illustrated. Price £34.50.

This book consists of 26 separate case histories which were published originally as monthly articles in *Anesthesiology News* over the past 3 years, from the Department of Anesthesia of the Albert Einstein College of Medicine in New York. These have been updated a little for the book version. Some of the contributors are Residents (the equivalent of Senior House Officers or Registrars in the U.K.), while others are staff members. Each author presents his or her own clinical case and each report has been subjected to the guidance of a Consultant or another senior expert, so the result is a very nice account of each problem, rather as one might find at a good Morbidity Meeting or Clinical Case Conference in the U.K. "Morbidity and Mortality (M&M)" meetings are notoriously difficult to make exciting, but the approach in this book is excellent, as each account is brief and succinct and the text is easy to understand. The reader can identify strongly with many of these case reports, so may be a little disappointed at the end to find that Dr Frost does not reveal the eventual outcome of the cases presented.

Each account is discussed for the anaesthetist in the context of the main medical or surgical problem. The individual case presentations are interesting and varied and include a number of intensive care problems. Those related to anaesthesia are followed by an anaesthetic assessment or an anaesthetic plan.

At the end of the book there is a set of 10 self-assessment questions which relate to each chapter. These are based on a single correct response to be selected from a choice of four possible replies to the statement forming the stem, so is unlike the M.C.Q. format used in the anaesthetic examinations set in the U.K. Although reviewers know that the result of criticizing M.C.Q. answers is often akin to shooting oneself in the foot, I would point out that some of the answers given as correct would be disputed as based on U.K. experiences of the problems set. However, this is not to detract from the value of these self-assessment exercises. In the U.S.A. this approach serves as "credits" of Continuing Medical Education towards the renewal of a licence to practice medicine. As peer review, quality assurance, quality control (or whatever be the term) are of concern to all of us at the present time, and will become increasingly so, the format of this book has obvious benefit.

The book is up-to-date and is recommended highly as good value for all anaesthetists. I look forward to the appearance in due course to another collection of such interesting cases.

Anthony P. Adams

Muscle Relaxants in Clinical Anaesthesia. By D. R. Bevan, J. C. Bevan and F. Donati. Published (1988) by Year Book Medical Publishers Inc., Chicago, London and Boca Raton. Pp.443; illustrated; indexed.

The Bevans and Dr Donati work in Montreal, where Griffiths introduced curare into clinical anaesthesia. It is thus appropriate that they should produce what will be recognized as a classic treatise on the clinical aspects of muscle relaxant drugs. The book starts with a brief history of the drugs and then reviews their physiology and the state of the art for clinical measurement. There are two excellent chapters giving the principles of pharmacodynamics and kinetics as they apply to the use of neuomuscular blocking drugs. The remainder of the book reviews the drugs, the reversal agents, the effects of disease, drug interactions, neuromuscular disease and malignant hyperthermia.

What is so splendid about the book is that it is not dogmatic. Where knowledge is incomplete, that is acknowledged. Look at the discussion as to the change in character of block with the prolonged use of suxamethonium.The virtues and the faults of pharmacokinetics are given. The whole book is well written and should be read by anyone with an intelligent interest in the blockers. Examination candidates will find in it all they need to know on this topic.

J. Norman

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